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STA Survey Study on the Development, Utilization, and Impact of Biotechnology

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CONTENTS

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[Report by the 4th Policy-Oriented Research Group of the National Institute of Science and Technology Policy of the Science and Technology Agency]

[Text]

I. Objectives and Methods of the Survey Study

1. Objectives of the Survey Study

Biotechnology is the name for the substance production technologies that utilize or copy living organisms or the functions of living organisms. There has been research into a wide range of areas from fundamental research in molecular biology, whence biotechnology had its origins, to industrial applications and research and development related to finding practical uses for these technologies. With this latter in particular, under way within the laboratories of a variety of private enterprises is research spanning a host of fields from fermentation and propagation technologies to the building of biochips from the functions of living organisms.

With the use and creation of resources for industrial applications at center stage, these practical applications of biotechnology are expected to have an epic-making impact on technology and economics. Hopes are high for even greater developments. Nevertheless, the current level of practical research is directly confronting several obstacles and technical problems. Moreover, the evaluation of the current status of research and development is made all the more difficult by conflicting opinions. While some hold the view that research has finally sobered up and gotten its feet on the ground, conversely others are saying that it has become difficult to ascertain the direction of research and development. Thus, a plethora of issues concerning the practical application of biotechnology remains even as industrial applications make gradual headway.

This survey study will focus attention on "practical applications" in particular. Survey analysis will cover research and development trends in biotechnology, examples of practical applications, and an overview of the genetic resources that will form the basis for future biotechnological research and development. Issues arising from such practical applications will also be studied.

2. Method of the Survey Study

A "Research Committee on the Development, Use and Effects of Biotechnology" was established to plan, analyze and carry out the survey study.

The composition of the members is as follows:

•"Research Committee on the Development, Use and Effects of Biotechnology"

In Japanese alphabetic order, titles omitted.

Committee Chairman

S. Tsumura (Taiyo Gyogyo Co. Research Institute, Advisor)

Committee Members

Hirofumi Uchimiya (Former University of Tsukuba Assistant Professor, currently Hokkaido University)

T. Kobayashi (Nagoya University, Professor)

T. Sakakura (Institute of Physical and Chemical Research, Principal Researcher)

T. Beppu (University of Tokyo, Professor)

E. Watanabe (Tokyo University of Fisheries, Assistant Professor)

Office

S. Sakamoto (The 4th Survey Study Group, General Senior Researcher)

T. Aoyanagi (The 4th Survey Study Group, (former) General Senior Researcher)

Y. Okazaki (The 4th Survey Study Group, (former) Senior Researcher)

K. Ushitani (The 4th Survey Study Group, Researcher)

Moreover, the Survey of the Current Status of Genetic Resources relies on the work of K. Kumagai, Guest Researcher (former head of Food and Agriculture Research and Development Association).

Besides reviewing the literature, the basic survey method was to conduct questionnaire and interview surveys of private businesses directly involved in the practical application of biotechnology. Summaries of the questionnaire and interview surveys are as follows:

•Questionnaire Survey

Persons surveyed: Research Managers from businesses doing biotechnology research and development 320 people

Return rate: 65.9% (number returned 211)

Survey topics: refer to the attached materials

To make the analysis easier, the results of the questionnaire survey were grouped together according to the industrial fields that represent the management responsibilities of the respondents (based on the responses to question 1) as is shown in Table I-1.

Moreover, the survey was conducted by commissioning to Japan Techno-Economics Society.

Table I-1. Representative Fields of Research Management and Responsibility of the Respondents

Field	Main number	Representative fields [() indicates internal number]
Pharmaceuticals	67	Pharmaceuticals: Production of pharmaceuticals, production of diagnostic drugs
Agriculture, Forestry & Fisheries	52	Agriculture and Forestry: Seeds and seedlings production and breeding, materials for agricultural chemicals and pesticides (45)
		Stock Raising: Propagation and breeding, pharmaceuticals for animals, feeds for animals (6)
		Fisheries: Propagation and breeding and pharmaceuticals for fisheries, feeds for fisheries (1)
Chemical Products	28	Chemical Products: Amino acids and organic acids and nucleic acid related, cosmetics and perfumes and coloring related, enzymes for industry, test drugs for bio-research
Food Products	34	Food Products: Sugars and proteins related, fermentation and brewing products, fats and oils related
Other	30	Mining and Energy: Bacteria leaching, energy related such as alcohol and methane (2)
		Electronics and Electricity: Bio-sensors, bio-elements (4)
		Machinery and Equipment: Equipment for bio-research, production systems (2)
		Environment: Waste water processing (13)
		Other: Paper and pulp (4), Other: No response, etc. (5)

*Interview Survey

Survey subjects: Companies making practical applications of biotechnology: 5 organizations

Principal survey topics:

(1) a summary of the operational and research system

(2) the technical content of examples of practical applications

(3) the particulars and background relating to the above

(4) opinions relating to the practical applications of biotechnology

(5) other special characteristics of biotechnology, etc.

II. Trends in the Research and Development of Biotechnology

1. A Summary of Research and Development Trends

In order to clarify the macro trends in biotechnology research and development, a database was made to chart the research and development trends in businesses that conduct biotechnology research and development. This database relies on such publications as "The 1989 Bio-Industry Annual" (CMC Company) and "The Nippon Keizei Sangyo Shimbun," etc. Specifically, the "research field" is based on the former, and the "number of researchers and research expenditures" was indexed according to the latter. Such data as "business category" and "capital" were assembled into a database for a total of 457 companies, and an analysis was made of research and development conditions.

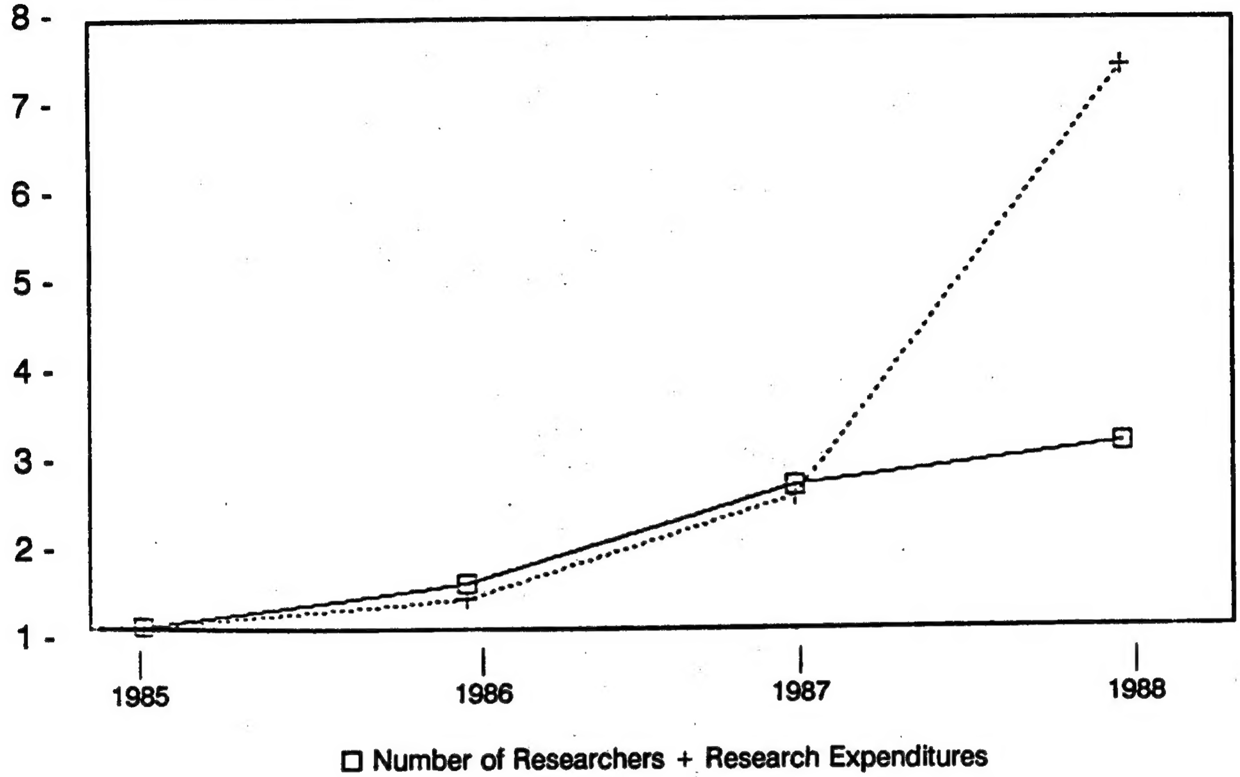
A shift occurred in the number of researchers and research expenditures in these private businesses as is shown in Table II-1 and Figure II-1. Both the number of researchers and the research expenditures as a whole increased at a rate of approximately 1.5 every year from 1985 to 1988. However, the growth rate fluctuated greatly from company to company, and this implies that business policies and conceptions regarding biotechnology research and development are quite diverse.

Table II-1. The Growth in the Number of Researchers and Research Expenditures for Biotechnology Related Research in Private Business

		1986/1985	1987/1986	1988/1987
Number of researchers	Average rate of growth	1.52	1.75	1.17
	(Standard deviation)	(2.04)	(2.83)	(0.70)
Research expenditures	Average rate of growth	1.32	1.91	2.95
	(Standard deviation)	(1.20)	(3.09)	(9.81)

Note: The average rate of growth is first calculated for each company per company for each year, and then the average is taken of that per year. Nevertheless, the number of companies included per year varies due to inconsistencies in the value (no responses, etc.).

FIGURE II-1 GROWTH IN THE NUMBER OF RESEARCHERS AND RESEARCH EXPENDITURES
(Taking the value of 1985 to be 1)



A correlation was found between the number of researchers and the business category as well as between the number of researches and capital as shown in Figure II-2 and Figure II-3. First, in business categories, the highest expansion in the number of researchers was seen in the pharmaceutical fields, followed by comparatively high trends indicated in such industry categories as mining, petroleum, energy, steel, metals, construction, electricity, and machinery. Moreover, when looking at classifications by capital, large-scale businesses with a capital of¥10 billion or more tended to have the highest rate of expansion.

On the other hand, the companies which are participating in biotechnology research and development are quite varied and the businesses they administer are highly diversified. Figure II-4 shows the participation in research field according to industry categories. According to this, there is a high correlation between the biotechnology research fields and the conventional business fields in the industrial categories of pharmaceuticals, agriculture, forestry, fisheries, livestock, horticulture, construction, electricity, and machinery. On the other hand, it was ascertained that research and development in a wide variety of fields such as biopharmaceuticals and biobotanicals is being conducted as new fields of research for such industries as mining, petroleum, energy, steel, metals, and other related industrial categories.

2. The Current Status of Genetic Resources (Summary)

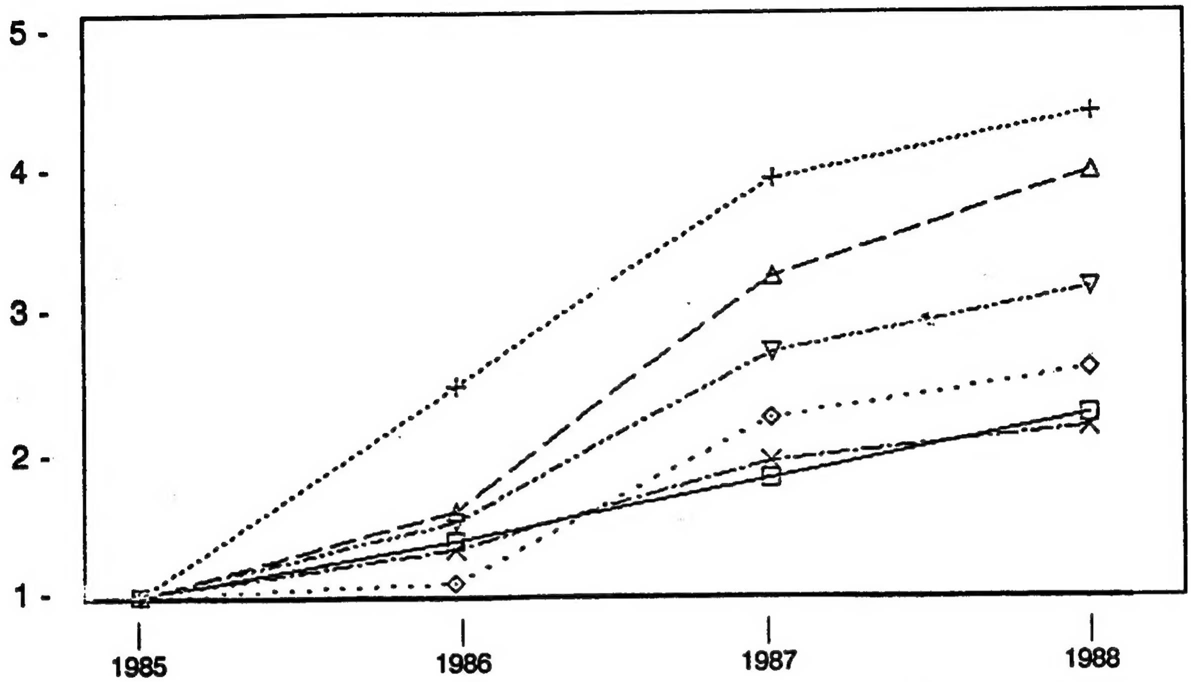
Next, the relationship between biotechnology and resources was studied from the perspective of the current status of the preservation and distribution of genetic resources.

The details of this, including shifts in national policy and future issues, are cited in a separate publication "Survey Report: The Current Status of Genetic Resources." Therefore, here we will simply touch upon conditions relating to preservation and use.

(1) The Preservation Conditions of Genetic Resources

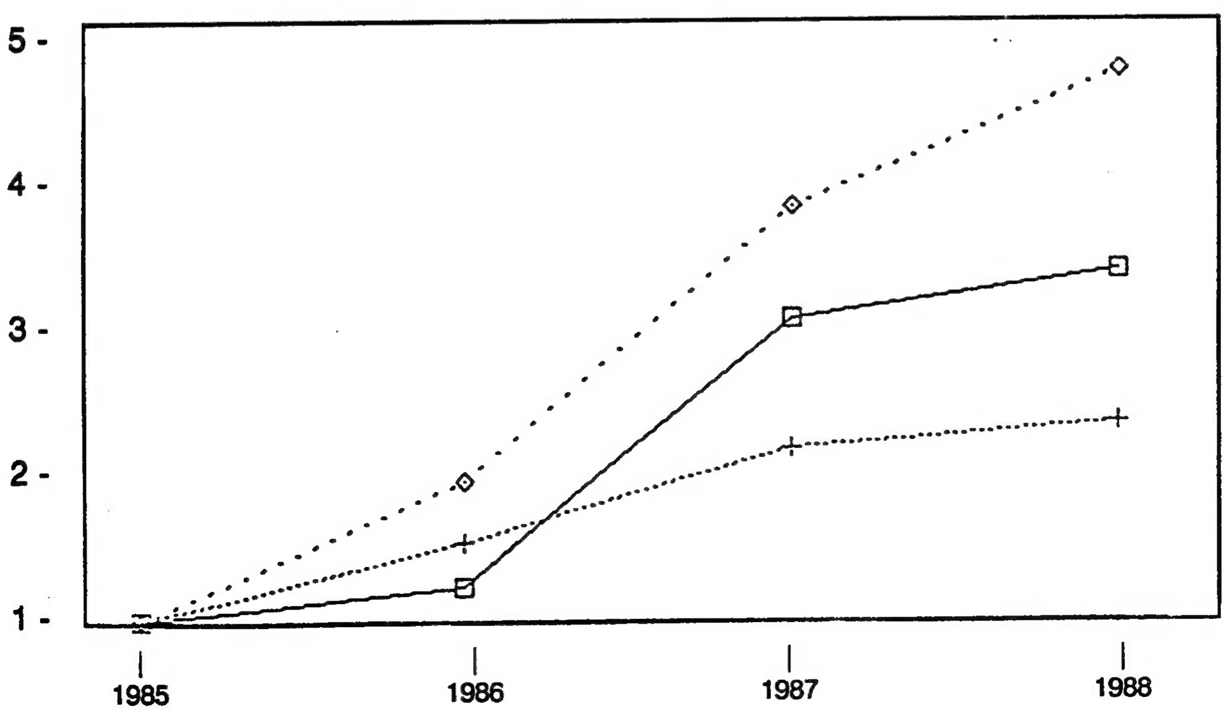
Beginning with the survey done by the Institute of Physical and Chemical Research in 1974, many organizations have conducted surveys relating to preservation conditions. Viewing them as a whole, they have become more organized and comprehensive with the subject

FIGURE II-2 GROWTH IN THE NUMBER OF RESEARCHERS BY INDUSTRY
(Taking the value of 1985 to be 1)



□ Chemical + Medical ◇ Food, Agriculture & Forestry & Fishery & Stock Raising & Horticulture
X Other ▽ Total
△ Mining & Petroleum & Energy & Steel & Metals
Construction & Electricity & Machinery and Equipment

FIGURE II-3 GROWTH IN THE NUMBER OF RESEARCHERS BY
CAPITAL INVESTMENT (Taking the value of 1985 to be 1)



□ Less than ¥1 billion + ¥1-10 billion ◇ ¥10 billion or more

matter of the survey gradually broadening and the contents becoming more detailed.

Because the subject matter and scope in all of these surveys varies, the number of genetic resources preserved for each kind of organism in the results of these surveys cannot be compared outright. For example, when looking at the number of seeds preserved at the National Institute of Agrobiological Research of the Ministry of Agriculture, Forestry and Fisheries, the numbers increased yearly from 34,025; 35,793; 38,090; 42,791; 47,981 to 54,175 in the years between 1983 and 1988. Moreover, the number of recorded strains at the Facility for the Preservation of Microorganism Varieties of the Institute of Physical and Chemical Research has steadily increased. Very broadly speaking, there has been an inexorable tendency to increase the number of items preserved for every kind of living organism (plant, animal, microorganism).

Next, the manner of preservation has taken a variety of forms corresponding to the type and characteristics of the target organism. This ranges from preservation as a group in order to maintain an ecosystem to preservation as individuals, seeds, organs and tissues, plant cells, culture tissues and cells, and DNA and RNA.

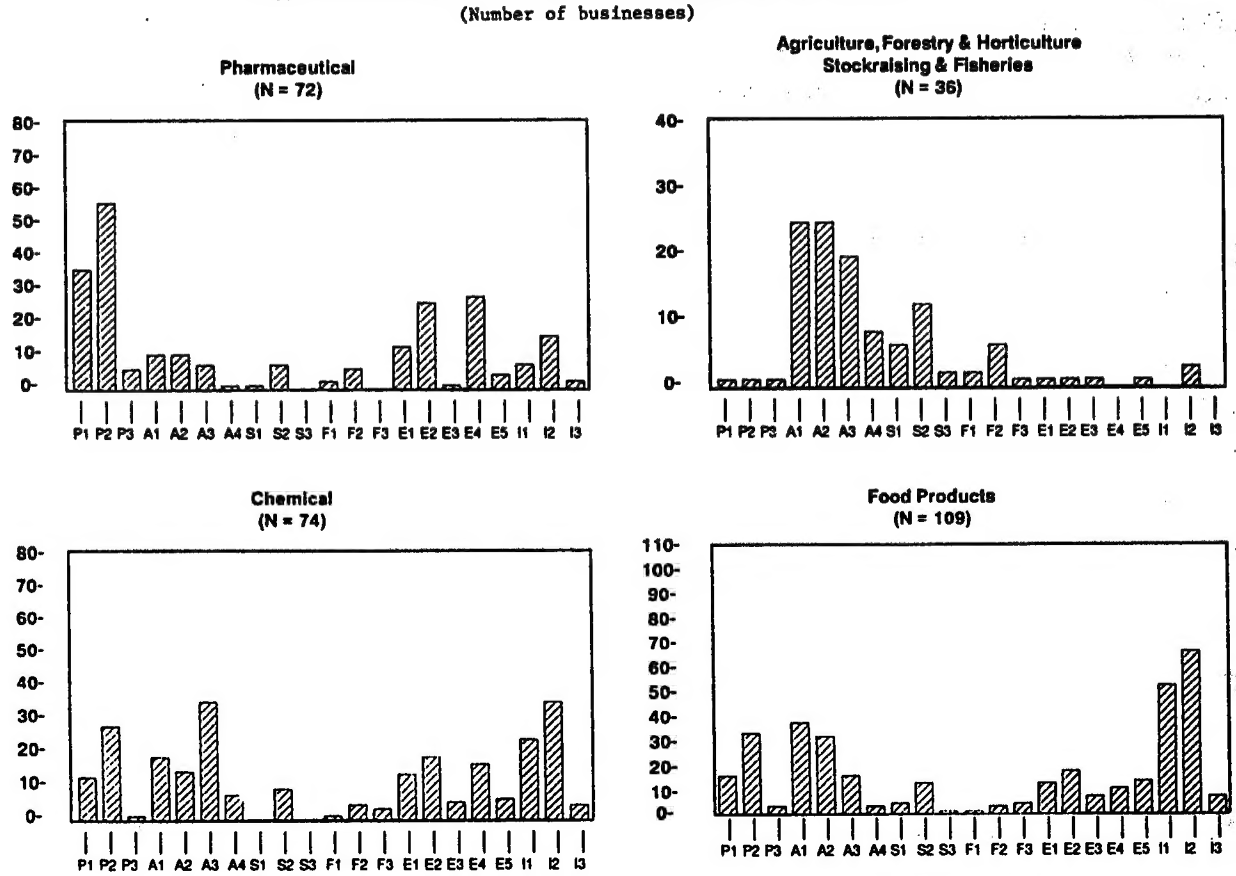
Furthermore, the technology of preservation corresponds to each of the forms of preservation, and thus preservation methods are extremely diverse. New preservation technologies are now being deployed. For example, there is the ultra low temperature freezing method that has recently come out from the great advances in cryobiology, and there is DNA and RNA level preservation by using genetic manipulation technology. While many technical issues still remain to be worked out, there are great expectations for future progress in research and development.

(2) Uses and Distribution of Genetic Resources

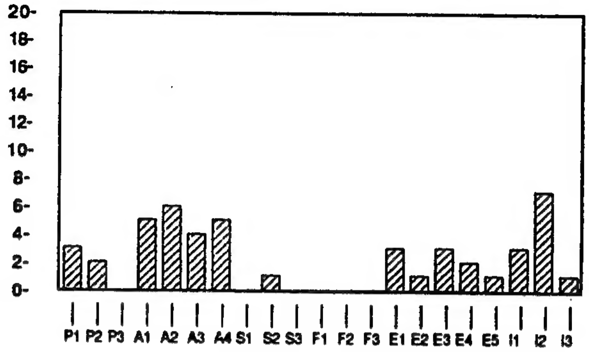
The use of genetic resources is necessary for fundamental scientific and technological research; it is of high use value for industry and for environmental protection; and it is anticipated that it will have other potential use values. Among these, industrial use is the most important area from the standpoint of using genetic resources. This is because industry is directly related to the production of resources necessary for human life. Food related fields, resource and energy related fields and chemical industry related fields all have a diversified range of uses. The key to their business success is the selection of seeds and strains that correspond to use objectives.

When considering these uses for genetic resources, the role of the systems which distribute and supply them is very important and expectations for them run very high. In Japan, the systems which preserve and supply genetic

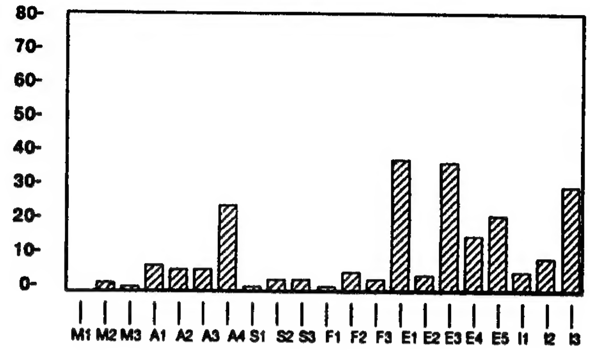
FIGURE II-4 FIELDS WHICH DEAL WITH BIOTECHNOLOGY BY INDUSTRY
(Number of businesses)



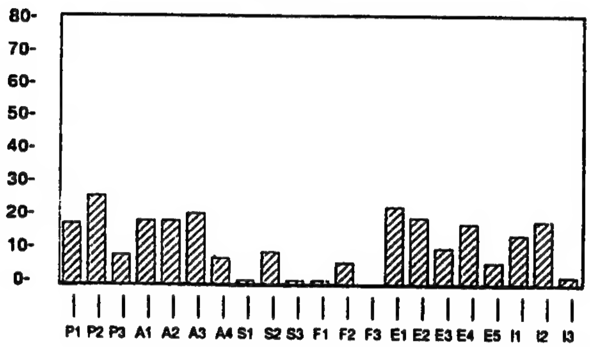
Mining • Energy • Steel • Metals
(N = 19)



Construction • Electricity • Machinery & Equipment
(N = 76)



Other
(N = 71)



(NOTE) The Key for the name codes of the bio-technology fields used in the horizontal axis of the figures appears below. These fields are based on the classification in "A Comprehensive Table of Bio-Tech Fields Within the Entire Bio-Tech Industry" (drawn up by the Industry and Economics Research Center, Inc.) found in Bio-Industry Yearbook: 1989 (CMC, Inc.), and they differ from the "Fields of Management and Responsibility" (Table I-1) which came from the questionnaire.

P: Bio-Pharmaceutical – P1: Bio-Pharmaceuticals; P2: Drugs under Clinical Study, Pharmaceutical intermediate products; P3: Information, systems, understanding and operation of genetics.

A: Agriculture Bio-Technology – A1: Plant bio-technology (tissue culture, etc.); A2: Seeds and seedings (production and sales, etc.), plant cultivation; A3: Plant culture materials, cultivation materials (agricultural chemicals, fertilizers, etc.), insects; A4: Agricultural machines, cultivating machines, horticulture, plants.

S: Stock Raising Bio-Technology – S1: Stock raising bio-technology; S2: Feed, pharmaceuticals for animals, experimental animals; S3: Stock raising equipment.

F: Fisheries Bio-Technology – F1: Fisheries bio-technology; F2: Feed, pharmaceuticals for fisheries, plant rearing, cultivation equipment; F3: Seaweed bio-technology.

E: Bio-Technology Equipment – E1: Bio-technology equipment, equipment for measurement and cultivation, etc.; E2: Experimental drugs, bacterial culture media, chemical carriers, blood serum, medical materials; E3: Clean rooms, clean room peripheral materials, bio-waste water processing, bio-reactors, compost, etc.; E4: Diagnostic and measurement equipment for information about living organisms, artificial organs, bio-materials, etc.; E5: Bio-electronics.

I: Industrial Bio-Technology – I1: Enzymes, immobilized enzymes; bio-technology materials for industry; I2: Chemical products, food products, health food products, drugs, cosmetics, energy, bacterial leaching; I3: Production reactors, systems, processing, biomass-energy, etc.

resources mainly belong to the various government ministries, agencies, and universities, and each does its work independently corresponding to the variety of organism, the importance of preservation, the use objectives, or the administrative classification.

Under these circumstances when organizations which preserve plant genetic resources were surveyed by the Science and Technology Agency in 1988 concerning the distribution of genetic resources, 68% (460) of the organizations targeted in the survey received inquiries relating to the supply and distribution of preserved plants. Moreover, the actual distribution records relating to plant genetic resources in the gene bank operations of the Ministry of Agriculture, Forestry and Fisheries showed an growth trend in the years from 1983 to 1988 with the number of transactions increasing from 122 to 175, 330, 282, 331, and 239; and the number of items increasing from 4,308 to 6,773; 6,510; 7,141; 12,138; and 5,745. The Facility for the Preservation of Microorganism Strains of the Institute of Physical and Chemical Research began actual lot sales of microorganisms in 1986, the number of lot sales thereafter increased at an accelerating pace (the number of lot sales in 1987 was 1,709 strains: 1,539 domestically, and 170 abroad). There were high expectations for the further distribution of these genetic resources.

Next, there is the problem of managing the data that is of primary concern for the use of genetic resources. At a minimum, the necessary information for genetic resources would be the genus name, the species name, and the name of the type or variety. Besides this, there could be a whole variety of information depending upon the preservation objectives and the use of the resources. For example, there could be passport data, management information for each species, genetic, physiological and morphological data, or physical, chemical and biochemical data.

According to the results of the previously mentioned survey by the Science and Technology Agency, 39.3% of the 491 responding organizations were recording only the plant name or the common name, and this was the highest response level. This was followed by agricultural data at 16.3%, passport data at 13.5%, genetic, physiological and

morphological data as well as physical, chemical and biochemical data at a total of 11.2% (the rest is omitted). It is difficult to assess whether these arrangements are progressing. Moreover, with the majority of responses concerning the method of management falling under a ledger of preservation (29.3%), a catalogue (23.3%), and a simple memo (18.7%), and even with future plans to use computers at 13.2% (among these 5.2% plan to use a database), the strong impression was given that as yet we are unprepared to modernize the management of information.

Furthermore, the goal of systematizing information management is not simply to make effective use of information in each organization, but it is also to supply necessary information to users in the general public. Under the present conditions, a prototype of a genetic resource information management system is being developed in part by each ministry and agency.

When considering the use conditions for the distribution of genetic resources and the form of information it will take in the future, it is difficult to say that it will eventually be brought together as a whole. However, it is expected that a number of problems concerning the management of genetic resources information will be resolved by the improvement and development of future hardware and software, the standardization of other survey items, and the creation of networks.

III. Practical Applications and Issues in Biotechnology (Results of the Questionnaire and Interview Surveys)

1. Practical Applications and Their Influence

The survey conducted by the Japanese Association of Industrial Fermentation is one way to express in numbers the future plans for the practical application of biotechnology. In this 1985 survey, the total projected market in the year 2000 for products which are applications of biotechnology is shown in Table III-1. Furthermore, the 1989 market for already existing bioproducts (limited to products related to genetic manipulation, cell fusion, and cell culture) is estimated to be approximately ¥118.7 billion (Nikkei Biotechnology Yearbook, 89/90), and such practical applications as α-interferon which utilizes genetic recombination technology and wines which utilize cell fusion technologies have already appeared.

Table III-1. The Market in the Year 2000 for Products Which Apply Biotechnology

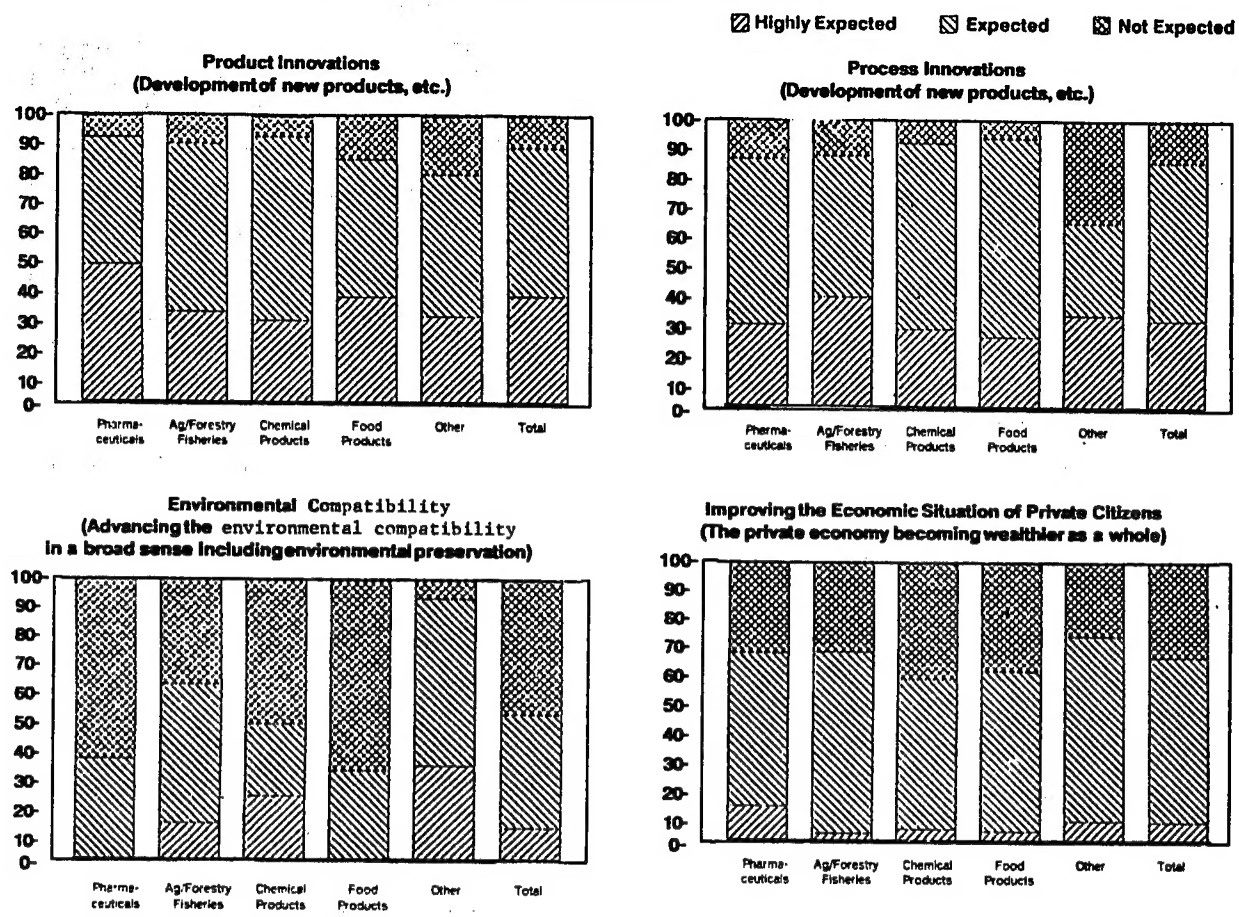
Industrial category		Market (¥ 100 million)
Agriculture, Forestry & Fisheries	Agriculture	14,014
	Stock raising	4,757
	Forestry	85
	Fisheries	1,181
Food industry		42,474
Paper & Pulp Industries		899
Electronics & Mechanical Industries		6,035
Chemical Industry	Basic chemical	15,221
	Chemicals	10,761
Pharmaceuticals & Agricultural Chemicals	Pharmaceuticals	31,514
	Agricultural chemicals	1,416
Resources, Energy, Utilities	Resources	3,345
	Energy	4,628
	Utilities	13,702

From survey materials of the Japanese Association of Industrial Fermentation

In our current questionnaire, the results of the question concerning expectations for the practical application of biotechnology are given in Figure III-1. When looking at the itemized figures, "increase in the knowledge and understanding of the living organism," "product innovations" and "process innovations" were cited as areas that can be expected to have practical applications (the total of "highly expected" and "expected"), and this was a very high response at approximately 90% of those surveyed. Although this cannot be called a clear-cut characteristic of any one particular field of research, the pharmaceutical field received "highly expected" responses concerning product innovations that were higher than the others, and thus this can be called somewhat characteristic of the pharmaceutical field.

In other items, "improving the economic situation of private citizens" and "improving Japan's position in the world economy" received an "expected" or better response from approximately 60%. Additionally, approximately half of the responses for "environmental optimization" and "effective use of resources" indicated the same. Of these, "environmental optimization" tended to vary between fields of research because it is directly linked to research content. Thus, while a high response was obtained in the environmentally related fields, that of the pharmaceutical and food product fields were low.

FIGURE III-1 EXPECTATIONS CONCERNING THE PRACTICAL APPLICATIONS OF BIOTECHNOLOGY (%)



Because "increase in the knowledge and understanding of living organisms" received extremely high responses, it can be said that one of the great characteristics of biotechnology is its aspect as a "knowledge" (or a "knowledge producing") technology.

Next, Figure III-2 shows the questionnaire results relating to the current perception of the practical applications of biotechnology from the standpoint of the degree to which the present state of biotechnology matches its future image. On the whole, more than half (approximately 55%) of those surveyed responded that the present state has a "comparatively high degree of practical application" or better (the total of "great degree of practical application" and "comparatively high degree of practical application"). When looking at the different research fields, the pharmaceutical field stood out in particular in its perception as being advanced in practical applications. This was followed by the fields of agriculture, forestry, and fisheries (however, among these the livestock field was not necessarily high). We suspect that these results reflect: the fact that α-interferon and hepatitis-B vaccine have already been manufactured and marketed in the pharmaceutical field; the fact that, although no specific products which utilize such technology as genetic recombination has yet come out in fields of agriculture, forestry and fisheries, the United States and others have developed open air testing; and the fact that such conventional technologies as tissue cultures will become highly influential. In fields other than these, responses of "comparatively high degree of practical application" or better and responses other than this were about fifty-fifty. Among these other fields, while there were extremely few responses, the tendency was toward a high perception that hardly any practical applications have been made in the fields of electronics and electricity.

In this way, biotechnology research managers in private enterprise gave a relatively forward looking evaluation of the current status in the practical application of biotechnology. Although there was a difference in technical achievements, progress in practical applications is being made in each field. Additionally, this view is not simply based on the specific products that have been manufactured and marketed, but rather on the fact that the new levels of knowledge characteristic of biotechnology have been reached one after the other.

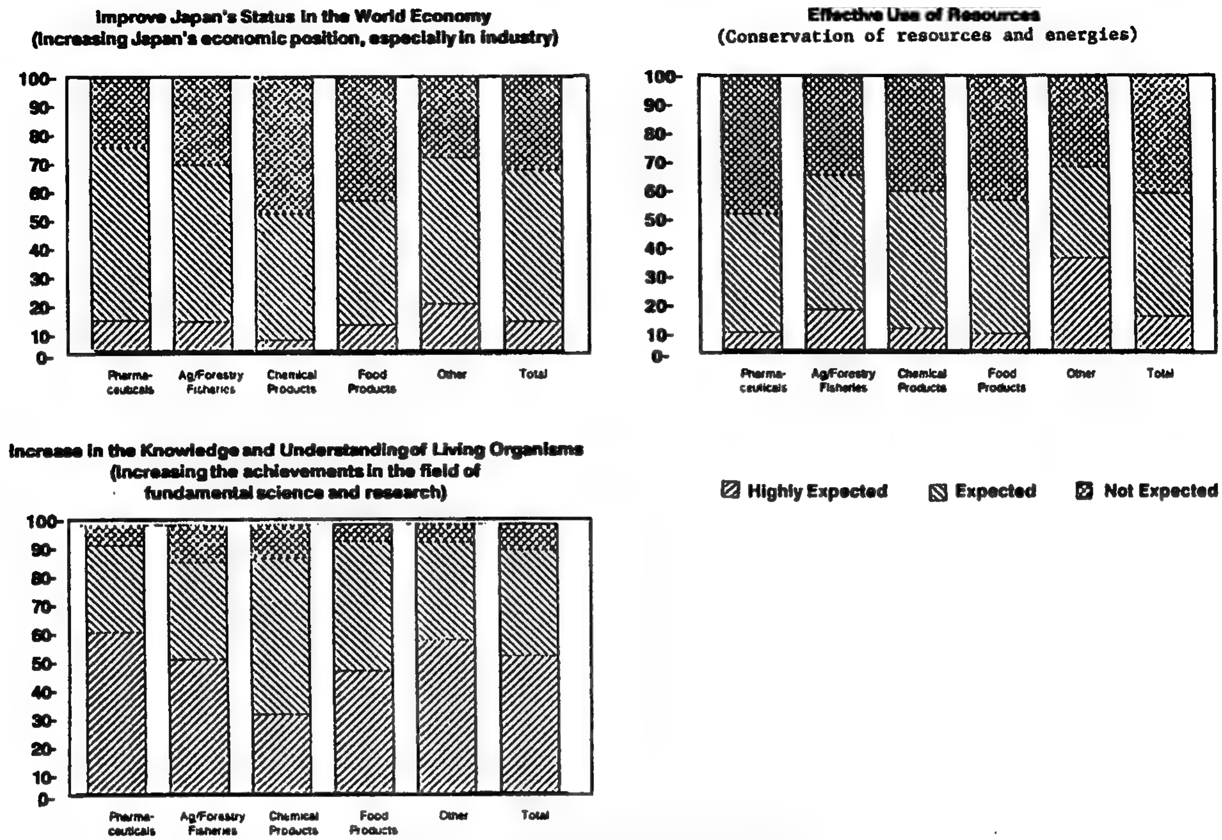
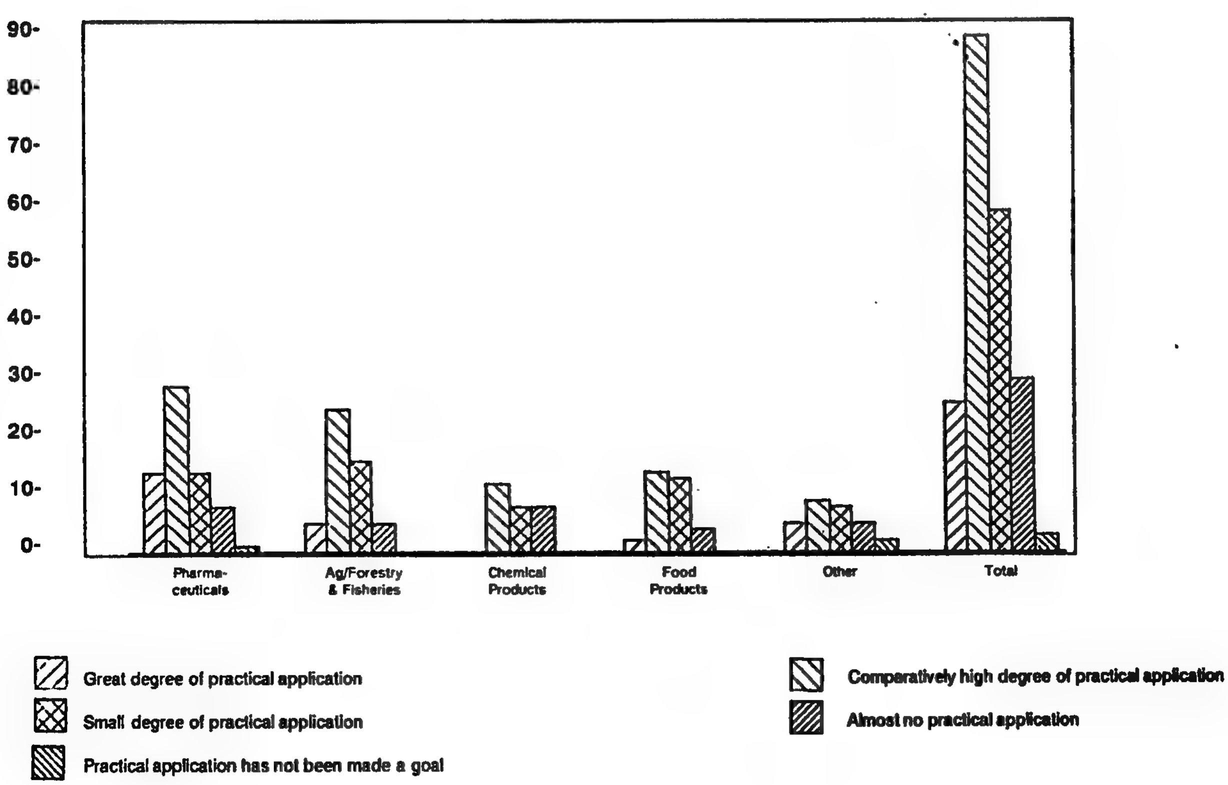


FIGURE III-2 DEGREE OF DEVELOPMENT TOWARD PRACTICAL APPLICATION
(Number of responses classified by field)



2. Practical Examples and Their Essential Features (Interview Survey)

(1) Hepatitis-B Vaccine (Kikuchi Laboratory of the Chemical and Blood Serum Therapy Research Institute, Inc.)

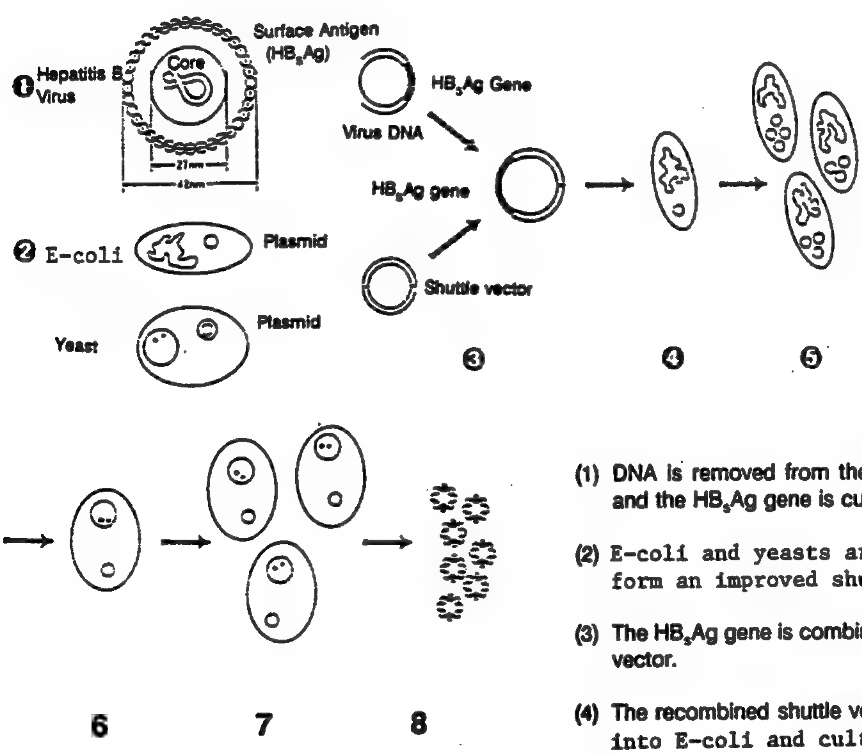
1) Technical Description

The hepatitis-B vaccine developed by the Chemical and Blood Serum Therapy Research Institute is Japan's first nationally produced vaccine made by genetic recombination. This is done by combining the genes (HBs genes) that make surface proteins (antigens) for virus particles that are put out by the hepatitis-B virus with an improved shuttle vector that is designed by combining the plasmids of *E-coli* and of yeast. This is multiplied in *E-coli* and finally, it is introduced into yeast where it is mass produced. A vaccine is made by separation and refining.

Compared to what is produced from the blood serum of the carrier, the vaccine that was made in the above manner is superior both in the quantity of supply and in safety.

2) Background to the Process and Practical Applications

METHOD FOR A RECOMBINATIVE GENETIC VACCINE USING YEAST HOST



(1) DNA is removed from the Hepatitis-B virus, and the HB_sAg gene is cut out.

(2) E-coli and yeasts are united to form an improved shuttle vector.

(3) The HB_sAg gene is combined into the shuttle vector.

(4) The recombined shuttle vector is introduced into E-coli and cultured.

(5) The shuttle vectors cultured in the E-coli are removed.

(6) The shuttle vectors are introduced into yeast, and cultured.

(7) HB_sAg is produced.

(8) The yeasts are destroyed and the HB_sAg is separated, refined and made into vaccine.

With Special Coordination Funds for Promoting Science and Technology, this research came about through participation in a research project (for 3 years from 1980) concerned with vaccines made via genetic recombination. The decision to allow the Chemical and Blood Serum Therapy Research Institute to participate was based on the fact that they had technical achievements related to conventional vaccines and on the fact that they had already unilaterally promoted the development of hepatitis-B vaccine from plasma sources.

This research was conducted in the form of joint research with Professor Matsuhara of Osaka University. Research that centered on the making of recombinants was conducted at the university (a researcher was sent from the Chemical and Blood Serum Therapy Research Institute). Meanwhile back at the Research Center, large quantities of the source virus were collected and refined. A large quantity of the resulting recombinants were cultured, antigens were refined, and verification sought.

Next, having succeeded at this, they were commissioned by the Research Corporation of Japan in 1983 to tackle practical applications. Besides the development of mass culture and stabilization technologies, they began to study plant level production and to develop the technology to make medicines. They succeeded in these practical applications in 1986, 1 year earlier than projected, and the products have been marketed since 1988.

Great pains were taken to maintain continuity in the technological developments at the Chemical and Blood Serum Therapy Research Institute. The extraction of the antigens alone without rendering them inactive was made possible by the earlier successes in protein refining technology that were gained from the development of a γ-globulin formula.

Then again, while tangible results were achieved by the research institute as outlined above, it should also be said that secondary benefits were made manifest by the opportunities afforded by the joint research between industry and academia. This linkage with academia has received high marks.

3) The Research System

In the beginning, the main responsibility of the foundation was the production and supply of the vaccine and the antiserum. Presently, its principal duties consist of research, production and supply of four kinds of substances: vaccines for use in the human body; vaccines for animals; formulations for various kinds of blood plasma; and experimental drugs for clinical investigations.

The Main Laboratory, the Kikuchi Laboratory, the Keicho Laboratory and the Aso Branch Laboratory make up a total of four research facilities. The Kikuchi Laboratory, which was newly built in 1985, concentrates approximately 70% of its energies on the research and development subdepartment where leading edge technical development is being conducted in such areas as biotechnology.

Among the 954 employees who make up the research system, there are approximately 140 researchers with primary duties. There are also approximately 90 production technicians and plant technicians in the production subdepartment. Among these, the personnel at the research subdepartment are mainly people who have completed the master's course or better. Moreover, annual research and development capital expenditures, including personnel expenses, is approximately ¥2 billion. Current research is focused on the previously mentioned four fields, and many themes are being taken up such as the study of bioactive substances.

(2) Senposai (Kirin Brewery Co. Ltd., Plant Research and Development Institute)

1) Technical Description

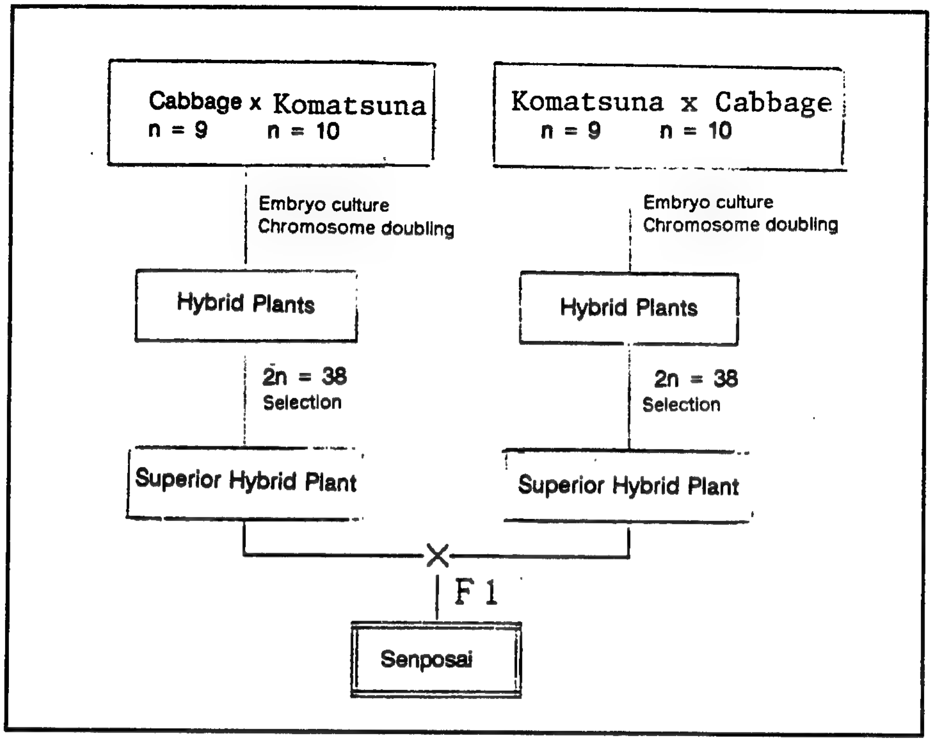
"Senposai" is a new hybrid grown using embryo culture technology. Specifically, after pollinating the hybrid embryos of cabbage x Komatsuna [a Japanese vegetable similar to spinach] and Komatsuna x cabbage (ordinarily these cannot be cultured as they are), a test tube embryo culture is made of each, chromosome doubling is performed on the hybrid seedling by colchicine processing. The strains which promise to be superior in cultivatability and product quality are selected from among these, and will be used as the crossbreed parents for F1 crossing.

"Senposai" combines the superior qualities of both cabbage and Komatsuna. It is a new kind of vegetable which is like a rapidly growing Komatsuna that is strong in summer heat and that has the fragrance and texture of a cabbage. In a normal year, it is the number one privately cultured bio-vegetable produced and supplied, and the market for it is quickly expanding. Seed sales goals have been set at ¥100 million.

2) Background of the Process and Practical Applications

First, during the development stage, Kirin Brewery Co., Ltd. joined forces with Tokita Nursery Co., Ltd. While Tokita Nursery Co., Ltd. took responsibility for supplying the genetic stock, for culturing and selecting in their plots, and for selecting seeds and making sales, etc., Kirin Brewery Co., Ltd. was in charge of developing the technology for embryo culture, and was responsible for establishing a strategic subdepartment for marketing, advertising, and sales. In the area of research and development, they built on their achievements in such fundamental areas of biotechnology as conventional varietal improvement techniques and tissue culture technologies. They overcame such technical issues in the field of embryo culture as determining the harvesting period for hybrid embryos and setting culture conditions, so that they achieved practical results in the short period of approximately four years from beginning research in 1983.

Next, in cooperation with the Hiroshima Prefecture Economic Alliance, which at the time was seeking a



candidate for a rotation crop and for a promising crop to represent them as the "Hiroshima Vegetable" Kirin Brewery was quickly successful in pioneering a production site and sales route for the culture and propagation of the new plant. In cooperation with the Economic Alliance and the Agricultural Association, they provided for a smooth development at the production site. They simultaneously prevented surpluses or deficits in supply and the collapse of prices by drafting cultivation manuals and shipping manuals, by providing instructions for planned production according to these, and by taking the stabilization of production and commerce into account. Meanwhile, they were simultaneously working with the University of Hiroshima and the Economic Alliance on cooking and processing, and they developed such items as senposai pickles and rice dishes. The development of these processed products was helpful in the regulation of demand for products as well as being effective in the building of name recognition for senposai.

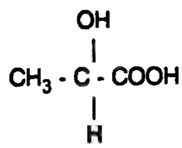
In this way, the building of a total system which did not confine itself simply to technical development, but included the culture, production, distribution and sales aspects can be considered one factor in successfully surmounting the handicaps involved in pioneering a market for a newcomer in the field of seeds and seedlings.

3) Research Systems

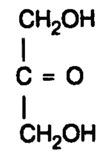
A scientific research laboratory was begun in the Yokohama plant in 1943. Later on, it was reorganized and further developed so that now the system related to biotechnology is roughly divided between the Research and Development Department (the Fundamental Technology Research Institute), the Pharmaceutical Operations Department (the Pharmaceutical Research and Development Laboratory, etc.) and the Agriculture and Biotechnology Operations Department (the Plant Research and Development Institute, and the Biofarm in Yamanashi). In all, when such subdepartments as beer, food products, and engineering are included, current research and development expenditures at approximately ¥15 billion have grown about tenfold that of a decade ago.

The Plant Subdepartment of Kirin Brewery has a 60+ year history of research on the cultivation of barley for beer and hops, and a 40+ year history for breeding and cultivation. From 1975 they began to consider entry into the field of seed and seeding biotechnology. After that they took up biotechnology in earnest. In 1983 they unified research functions that had been distributed among their various plant sites, and established a resource research laboratory. This was given its current name of the Plant Research and Development Institute in 1986.

The Plant Research and Development Institute, including the employees stationed at the Fundamental Technology Research Institute and the Beer Operations Department, currently harbors a staff of approximately 100 people (of these approximately 45 are researchers). Besides the improvement of barley and hops varieties used as raw materials for beer, they have taken up research and development of such plants as rice, potatoes, vegetables, and flowers that have been subjected to



(D-2-hydroxy propionic acid
D - Lactic Acid



Dihydroxy Acetone

tissue culture, cell fusion, and genetic manipulation. These activities have centered on the application and development of research related to practical uses.

Kirin Brewery joined in many joint research projects in this R&D, and they formed business ties with nursery companies, other domestic private enterprises, universities, public testing and research organizations, and even foreign enterprises. They have participated in several national projects such as the development of a culture seedling production system for rice.

(3) D-Lactic Acid, Dihydroxy Acetone (Daicel Chemical Industries, Co., Ltd., General Research Institute, Biochemistry Laboratory)

1) Technical Description

Lactic acids are widely used as raw materials in food products, pharmaceutical products, and chemical products. Among these, D-lactic acid is used as an intermediate substance in the production of agricultural chemicals. Specifically, the D-lactic acids developed by Daicel Chemical Industries is a substance that produces only highly pure D-lactic acid. This is done by fermentation with the Sporolactobacillus sp. which is a D-lactic acid producing bacterium. By displacing the hydroxide group of the D-lactic acid with chlorine, L-type α-chloropropionic acid is produced, and as previously stated this is supplied as a raw material for agricultural chemicals.

On the other hand, D-hydroxy acetone is a substance that is produced in oxidative fermentation by the acetic acid bacteria with glycerine as the raw material, and it is a chemical substance that is used as a raw material in cosmetics, etc.

2) Background of the Process and Practical Applications

The research opportunities for D-lactic acid and dihydroxy acetone arise from user demands. We will describe D-lactic acid in the following.

The α-chloropropionic acid (D,L types) described above is normally supplied to users as a raw material for agricultural chemicals by using conventional chemical compounding methods. However, when used as the raw material for herbicides, the D type is inactive compared to the activity expressed by the L type chloropropionic acid, and thus users requested through the Organic Compound Operations Department of Daicel Chemical Industries that the research laboratory supply only the L type. Initially, the research laboratory approved this via optic resolution, but half of the worthless D type remained. They then focused attention on the precursor lactic acid, and began to investigate the lactic acid bacteria that produced the D-lactic acids used to obtain L type chloropropionic acid.

In taking up this investigation the technology for the lactic acid fermentation system was extremely old, and their assumptions about the bacteria were relatively simple. Receiving transfer cultures from American Type Culture Collection (ATCC), DSM, and universities with which they had long standing ties, they discovered among these strains a lactic acid bacteria that was highly pure and produced only D-lactic acid. This did not pose any particular technical problems for the fermentation plant in terms of established technology, and they were able to meet user needs in the extremely short period of about one year of research and about a half year of study into increasing the scale at the plant.

Furthermore, in order to develop this even further, they conducted joint research with Nagoya University to study production in a bioreactor, and were successful in the development of a provisional technology. In addition to requiring a further technical breakthrough in dealing with the problem of production of purity in bioreactors (the intrusion of L-lactic acid), fundamental problems were posed by costs, and by the fact that demand for D-lactic acid itself is not large. This has resulted in the bioreactor not currently being on line.

3) Research System

Formerly Dainippon Celluloid, a manufacturer of celluloid, Daicel Chemical Industries is currently a major chemical manufacturer of products related to cellulose such as cellulose acetate which is derived from celluloid, as well as acetate organic compound products including gun powder, plastics, and film related products.

The research system is arranged into two laboratories, the General Laboratory which is the center for the Research Department and the Tsukuba Research Laboratory. Moveover, both of the laboratories have biochemical research labs as suborganizations of the General Research Laboratory and a Technical Development Department is established at each factory. The research staff is about 800 people strong, and research expenditures have reached about ¥10 billion (about 4% of sales). Besides Biochemical Research Laboratory, research related to biotechnology is also conducted at the Tsukuba Research Laboratory and the Arai Factory, etc., and has a staff of approximately 50 people including those in the main department. Moreover, bioresearch was taken up in around 1969. Since then they have taken up the study of the chemical processes in fermentation by microorganisms and they have developed research whose principal goal is to create new synthetic processes.

(4) Fructo-Oligosaccharides (the Biological Science Research Institute of Meiji Seika Co., Ltd.)

1) Technical Description

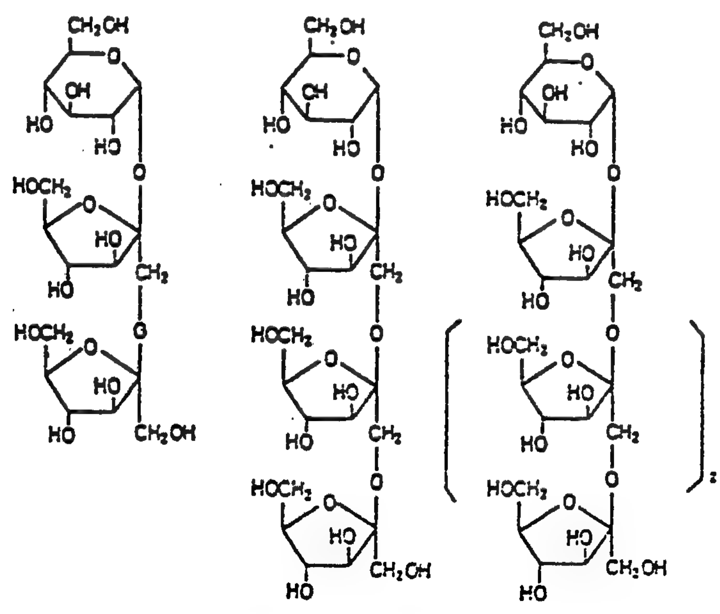
Fructo-oligosaccharides are sugars in which one to three molecules of fructose are bound to the fructose portion of sucrose, and their principal characteristics and functions are low spoilage, low digestibility, effective in the increase in the bifidobacterium, improve fatty substances, and improve constipation. Currently, fructo-oligosaccharides make good use of these effects and are widely used as sweeteners in food products and additives to animal feeds.

At their research laboratory, Meiji Seika clarified the superior functions of these oligosaccharides and developed methods to industrially produce them. They were able to produce the first practical applications in 1983. This is an example of the world's first successful development of a sugar having these physiological functions.

In the manufacturing process, highly concentrated liquid sucrose is allowed to react as needed with solidified fructose transferase (or with the cell) which are produced from cultured A. Niger. The fructo-oligosaccharides are produced in a bioreactor.

2) Background of the Process and Practical Applications

Meiji Seika set about obtaining oligosaccharides in 1979. They took this opportunity to begin searching for effective sweeteners that could replace sucrose (for substances that provide the good features of sucrose and suppress the bad ones). First, they looked for a substance which would not promote tooth decay. Then, they pursued thorough research into the substance from the point of view of physiology, and were the first to clarify the



1-kestose (GF$_2$) nystose (GF$_3$) 1^F-β-fructofuranosyl nystose (GF$_4$)

Chemical Structure of Fructo-Oligosaccharide

practical properties of oligosaccharides from their low digestibility to their effective improvement of intestinal flora. Meiji Seika was the hub of an investigation that established a research committee of specialists from differing kinds of fields such as sugar chemistry, medicine, and threpsology who were brought together to clarify the properties of oligosaccharides. Resulting from these efforts, the first products went on sale in 1983. The effectiveness of oligosaccharides in livestock is due to an increase in feed efficiency by improving intestinal flora, and when this became clear, sales as a product for stock raising began in 1984, as a product for pets in the following year. Currently, business is booming with production spreading abroad, and joint ventures being established in Europe and the United States.

In this instance of practical application, rather than simply focusing on the sale of a single product, physiological functionality in food ingredients was discovered and pursued. Consequently, there is clearly a great significance in becoming the pioneer to exploit a new field in food products. In the background to this, the company was used as a hub to gather experts in a variety of specialized fields in order to develop understanding for each issue that came up. In this process of developing experimental methods and ways of bringing data together, such efforts at self-help were undertaken as the establishment of a research committee to provide a forum for the exchange of this information. This practical application created the so-called oligosaccharide boom.

3) Research Systems

In addition to the Biological Science Research Institute, there are: the Foods Development Research Laboratory responsible for research development of candies and food products; the Investigative Research Laboratory, a subdepartment responsible for the field of medicine; the Research Laboratory for Agricultural and Stock Raising Drugs; and the General Pharmaceuticals Research Institute which is composed of the Safety Laboratory, etc. Moreover, there are approximately 800 to 900 researchers at all the research institutes (with a total staff of approximately 5,000 workers).

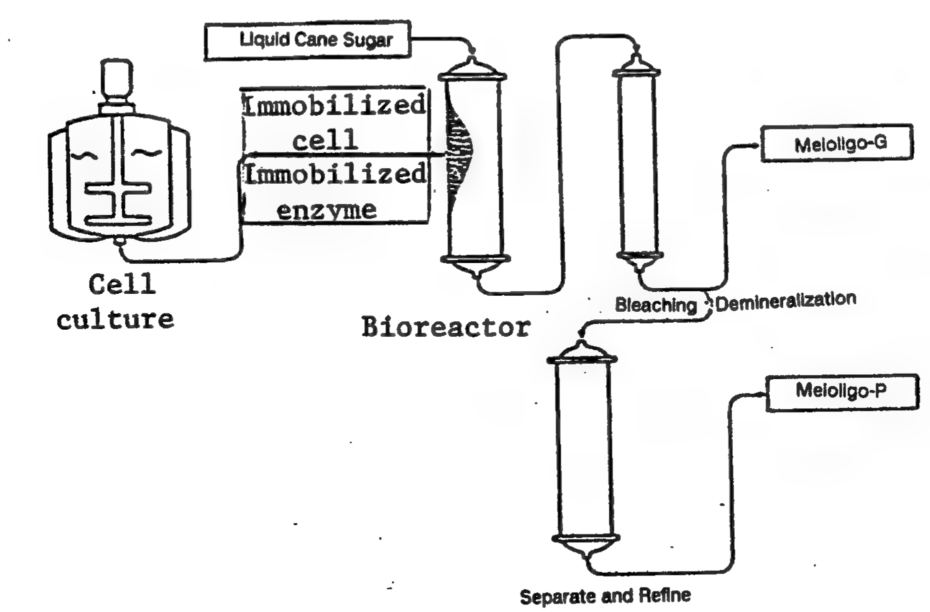
The Biological Science Research Institute is conducting research that centers on biotechnology in fields that merely touch upon or are unrelated to pure medicine or pure food products. It has approximately 55 researchers.

(5) Biological Oxygen Demand (BOD) Sensors (Denki Kagaku Keiki Co., Ltd., Development Department)

1) Technical Description

BOD is a water pollution index for rivers and industrial waste waters, etc., and with conventional methods this measurement entails a complicated five day operation.

The BOD microorganism sensor developed by Denki Kagaku Keiki Co., Ltd., targets soluble BOD (soluble organic substances). It is made by enclosing a yeast (Trichosporon cutaneum) in a hydrophilic acetyl cellulose membrane, and by equipping the tip of this with an



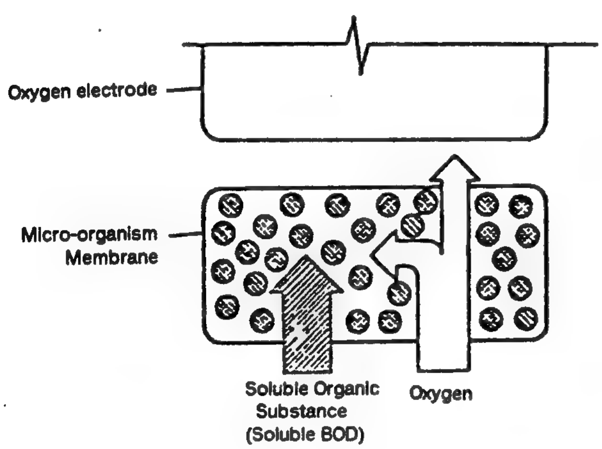
Outline of the Industrial Production of Frutco-Oligosaccharide

oxygen electrode. When a solution containing soluble BOD (the test material) permeates the membrane, the oxygen is consumed by the enclosed microorganism. The oxygen concentration reaching the electrode is thus reduced, and the soluble BOD is measured by its mutual relationship with the quantity of this reduction. The development of this sensor makes it possible to measure BOD within 20 minutes.

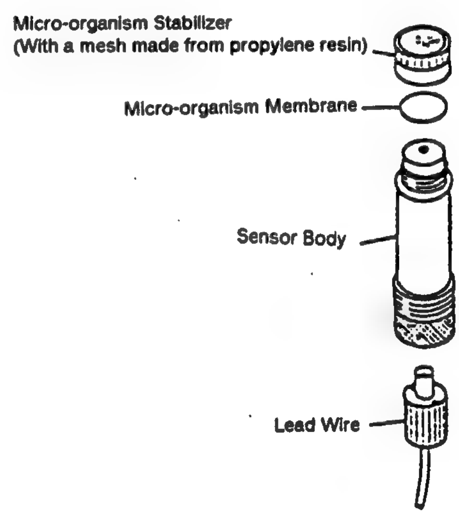
2) Background to the Process and Practical Applications

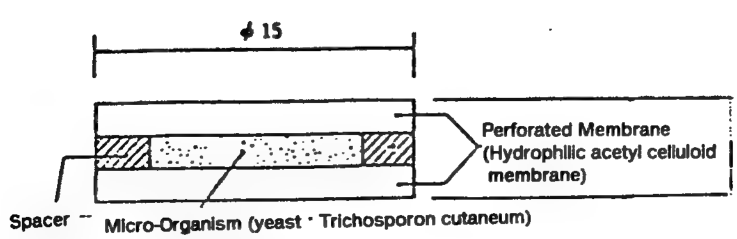
The development of biosensors was undertaken approximately 10 years ago when a variety of reports related to biosensors began to appear at academic conferences at around that time. Before then, Denki Kagaku Keiki only targeted "inorganic" systems, but afterwards, for the first time, they began to target "organic substances." In this latter development, they received technical assistance from the Resource Science Research Institute of the Tokyo Institute of Technology. They worked this input into practical applications by using sensor technology that had previously been developed by their own company. Denki Kagaku Keiki was the first company to develop an electrode for a microorganism sensor that combined an oxygen electrode and a microorganism membrane.

During the development of this biosensor, the company introduced the fundamental research results from universities and other businesses (such as food manufacturers) and with their own sensor technology, conducted research and development that closely followed such product stages as follow-up verification, designing the instrument, and establishing the system.



Principle of a BOD Sensor





Structure of the Micro-Organism Membrane for Measuring BOD

Furthermore, as for microorganism sensors used to measure substances other than BOD, they have already made available their own for practical application, targeted for ethyl alcohol and acetate. Additionally, they are currently taking up the development of instruments to measure the number of putrefying bacteria in food products and of instruments which measure a sort of "taste," combining several kinds of sensors.

3) Research Systems

The company, whose primary interest lies in analytic and measurement instrumentation, was established as the Electrochemical Instrumentation Research Institute in 1945. It undertook the manufacture of Japan's first pH electrode, followed this by developing an ion electrode, and then arrived at its current project. Technical development is centered in the Development Department (approximately 50 people).

The objective of biosensors is to measure what cannot be measured chemically, and the percentage this occupies in measurement device as a whole is extremely small.

3. Issues Related to Practical Applications

(1) Problems in Practical Applications

Responses to the "problems (obstacles) confronting practical applications" in the questionnaire survey are shown in Figure III-3.

In these results, the response which occurred most often as a whole was "research in fundamental fields is not yet sufficient." The definition of this so-called "fundamental research" is under debate, but one representative property of its content would be the "pursuit of scientific principles;" another would be "searching for seeds;" and to these can be added the characteristic "long-term research."

This survey also included such question as the types of fundamental research necessary to promote practical applications of biotechnology in the future. The results are shown in Figure III-4. According to these, "clarification of biological functions and structures," "investigating (screening) new functions and structures of organisms," and "development of new research methods" were given in that order. In the fields of chemical products and food products, however, the highest response was "screening new functions and structures."

Moreover, according to a separate survey conducted by the Science and Technology Agency concerning fundamental research, there was strong recognition that fundamental research into the life sciences, including biotechnology, has fallen behind internationally, especially compared to the United States. Results indicated that compared to other fields, the percentage of research managers and researchers who hold to the theory that "Japan is getting a free ride in fundamental research" is quite high (refer to Figure III-5).

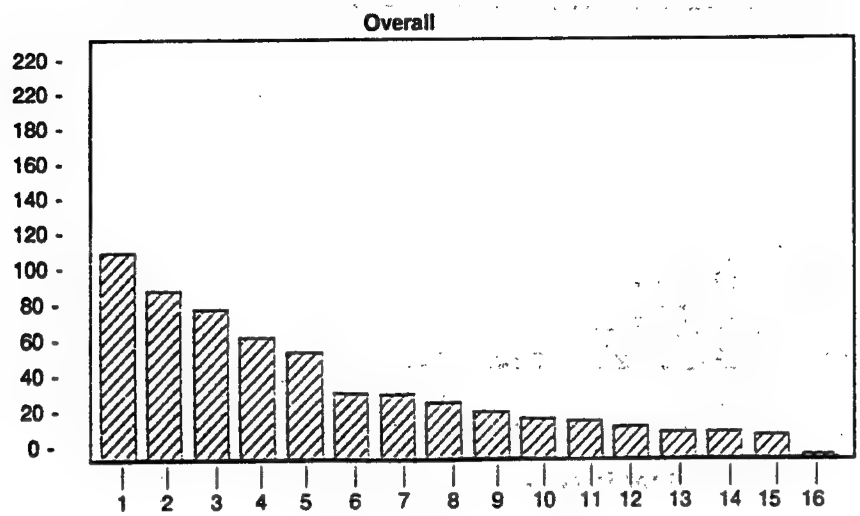
With this in the background, the results obtained concerning the conditions for conducting fundamental research in the appropriate research fields related to the businesses targeted by the questionnaire survey are shown in Figure III-6. Close to 60% of the responses indicated that they were in the preparatory stages of undertaking fundamental research, and moreover, more than 80% plan to do so in the future. In addition, compared to other fields, there was a tendency for more research to be conducted in pharmaceuticals, and more than half of all the fields responded that "we are already conducting research." In recent years there has been high recognition of the importance of fundamental research even among private enterprises. The strengthening of fundamental research subdepartments such as the establishment of the Fundamental Research Laboratory is being promoted, and these results are thought to indicate one aspect of the most recent tendencies.

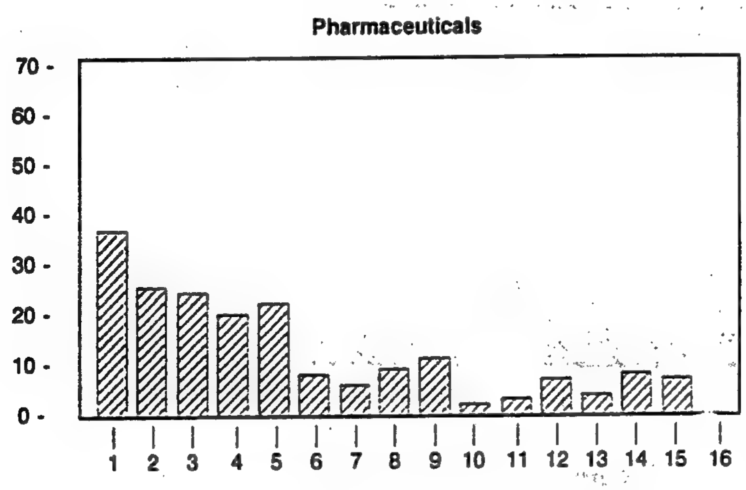
Meanwhile, the questionnaire survey asked the research managers for their opinions concerning the conduct and promotion of fundamental research within their own company (refer to Figure III-7), and the greatest number of responses said "we feel the necessity for this, and the preparation of a joint research system with domestic universities and public research institutes is necessary." This means that while strengthening the fundamental research, the private enterprises rely on the long standing expectation that the universities (or the national and public research institutes) bear this burden. In a certain sense, this indicates the difference between industry and academia concerning the content and characteristics of fundamental research. Next came "many superior research personnel" and "unified intra-business policies." About 13% responded "this is the nature of the research conducted at universities and national and public research institutes, and we do not necessarily feel that it should be conducted in our company."

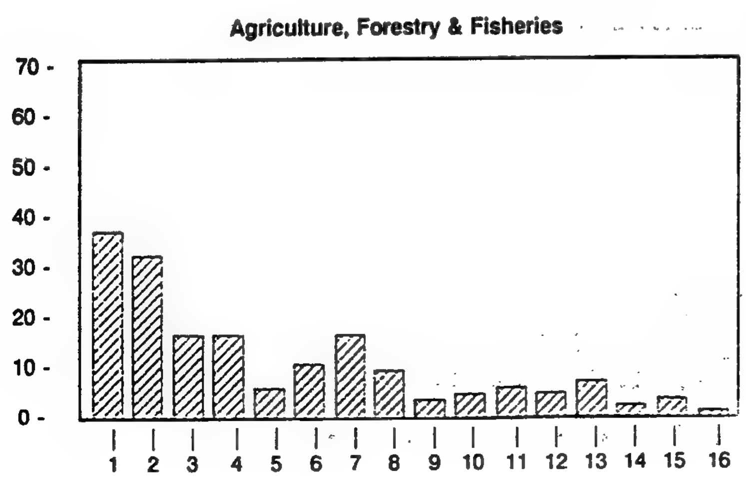
The next most frequently cited problem in practical applications was: "There are limitations to the independent practical application of biotechnology." That is, when making practical applications of biotechnology in general: (1) biotechnology needs to be incorporated as one part of an already existing production process for chemical or food products, etc.; and (2) it is necessary to construct systems that not only depend on fundamental biotechnology, such as genetic recombination and cell fusion technologies, but that also integrate new production processes such as separation and refining technology. This response indicates that the compatibility of already existing processes and the development of new processing technologies have hit a bottleneck. (This was the most cited response in the field of food products.)

Next came "research in the fields of application and development are not yet sufficient." This very frequent response (37% in all) was given in relationship to research fields directly involved in practical applications and not just in relationship to fundamental research. Moreover, this was the most frequent response cited in the chemical field.

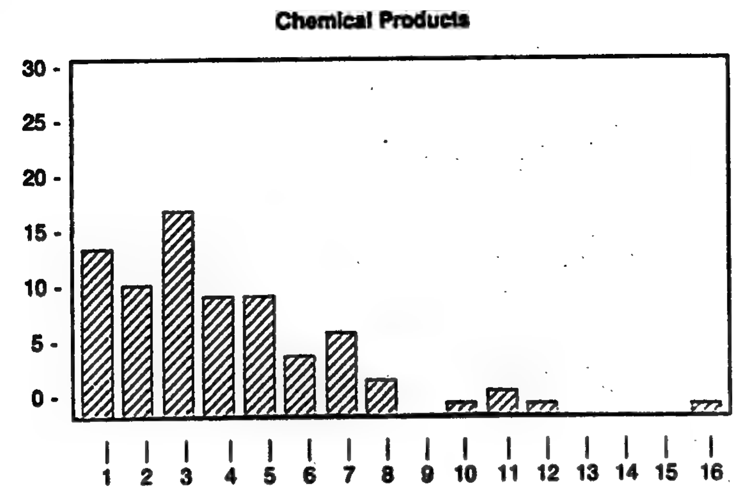
FIGURE III-3 PROBLEMS CONFRONTING PRACTICAL APPLICATIONS

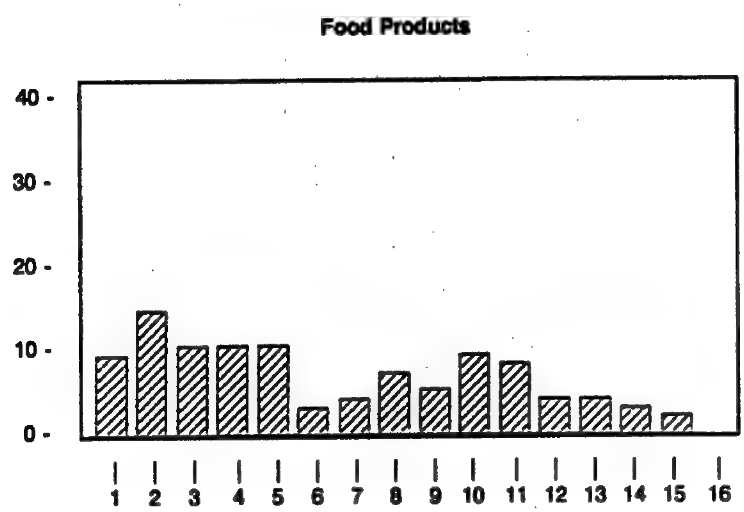


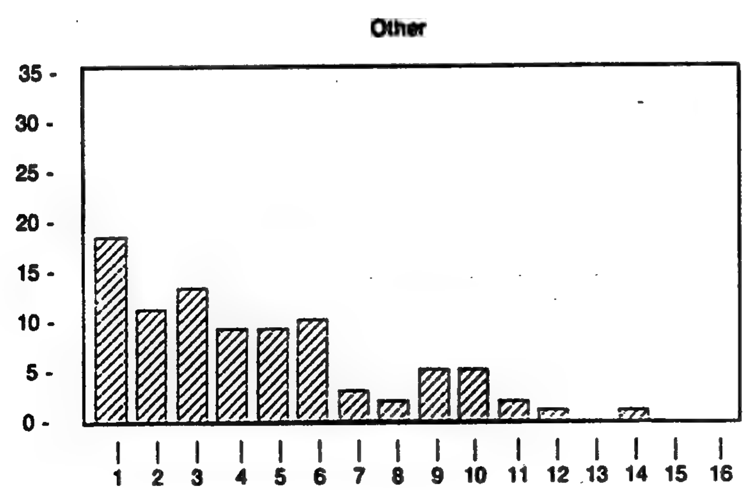




1. Research is not yet sufficient in the fundamental fields.
2. There are limits to making practical applications of independent biotechnology.
3. Research is not yet sufficient in the fields of application and development.
4. There is not enough research personnel.
5. Marketability is unknown.
6. The quality of research personnel is still low.
7. There are few useful genetic resources, or they are unknown.
8. Research facility improvements are insufficient.
9. Existing regulations & systems are not appropriate for the advancement of biotechnology research in general.
10. Safety regulations and systems have not yet been established.
11. There has been no building of public acceptance.
12. Safety regulations and systems are too strict.
13. There is not enough research capital.
14. Intellectual property rights such as patents have not been established in legal system.
15. The system of cooperation between industry, academia, and government is insufficient.
16. Other.







1. Research is not yet sufficient in the fundamental fields.
2. There are limits to making practical applications by biotechnology, alone.
3. Research is not yet sufficient in the fields of application and development.
4. There is not enough research personnel.
5. Marketability is unknown.
6. The quality of research personnel is still low.
7. There are few useful genetic resources, or they are unknown.
8. Research facility updating is insufficient.
9. Existing regulations and systems are not appropriate for the advancement of biotechnology research in general.
10. Safety regulations and systems have not yet been established.
11. There has been no building of public acceptance.
12. Safety regulations and systems are too strict.
13. There is not enough research capital.
14. Intellectual property rights such as patents have not been established in the legal system.
15. The system of cooperation between industry, academia and government is insufficient.
16. Other.

FIGURE III-4 FIELDS IN WHICH FUNDAMENTAL RESEARCH IS NECESSARY

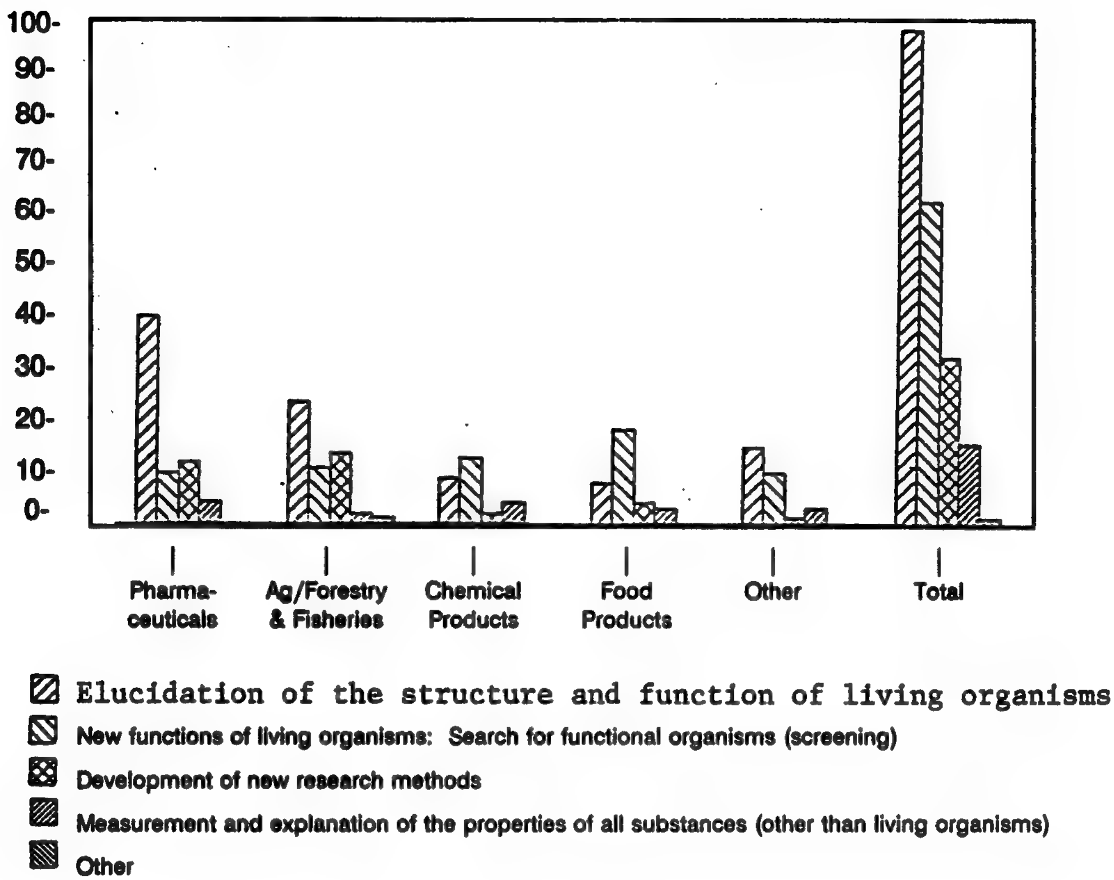
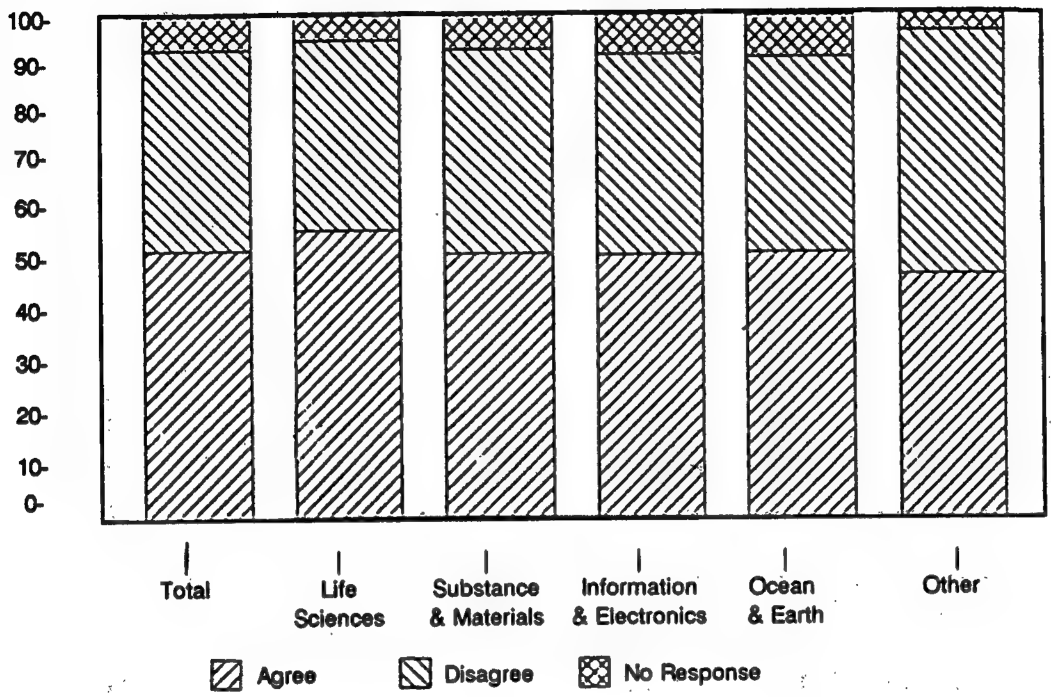
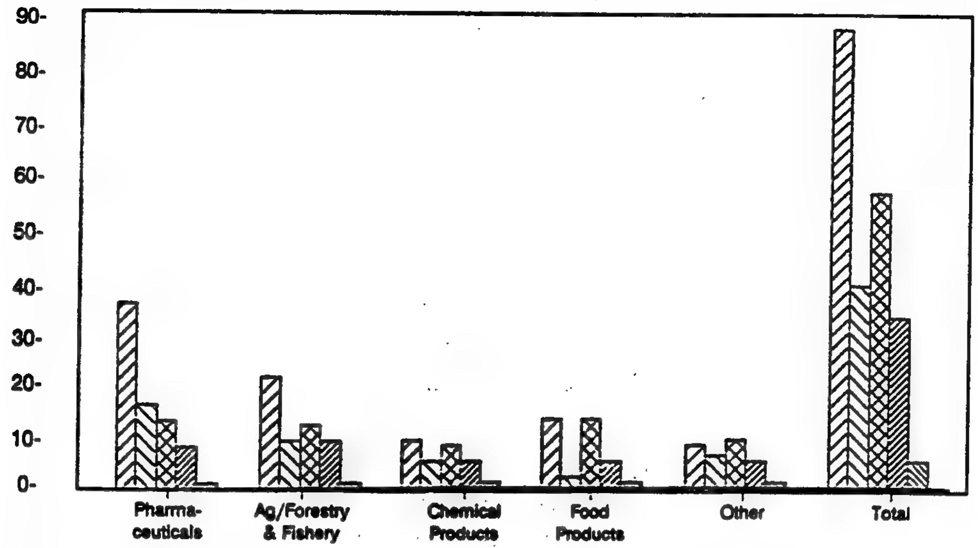


FIGURE III-5 ACCEPTANCE OF THE "FREE RIDE IN FUNDAMENTAL RESEARCH" THEORY
(Categorized by Research Field: %)



Source: "Fundamental Research and the Basis of Research: A Survey Report on the Research Environment" (Science and Technology Agency)

FIGURE III-6 CONDUCTING FUNDAMENTAL RESEARCH



Already conducting fundamental scientific research.

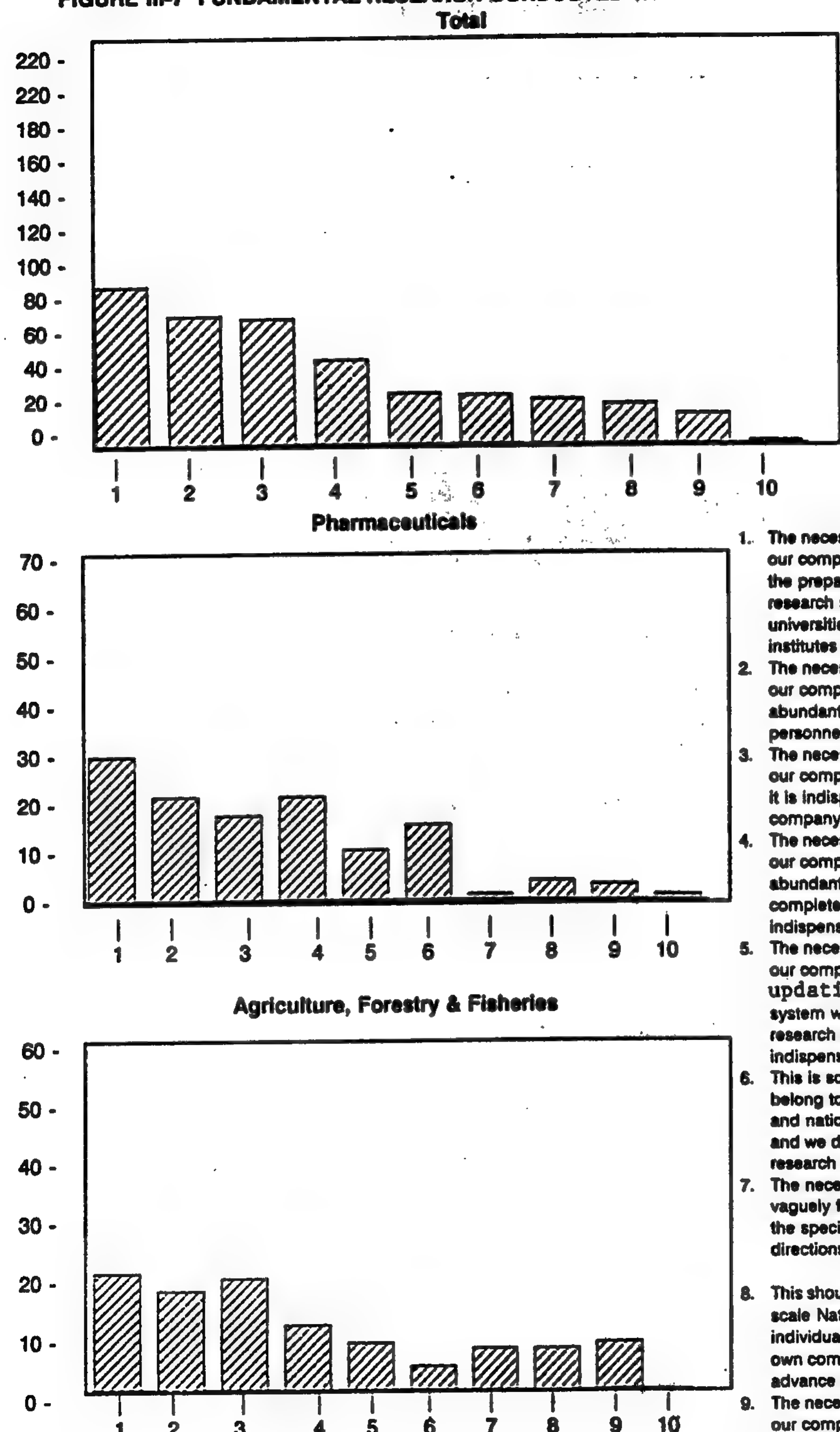
Preparatory stages for conducting fundamental scientific research.

Currently no fundamental scientific research, including the preparatory stages is being conducted, but there are plans to do so in the future.

Currently, no fundamental scientific research is being conducted and there are no plans to do so in the future.

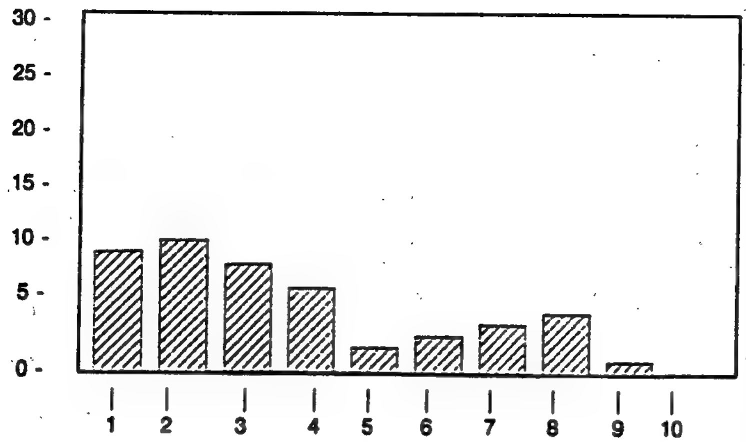
Other

FIGURE III-7 FUNDAMENTAL RESEARCH CONDUCTED WITHIN THE COMPANY

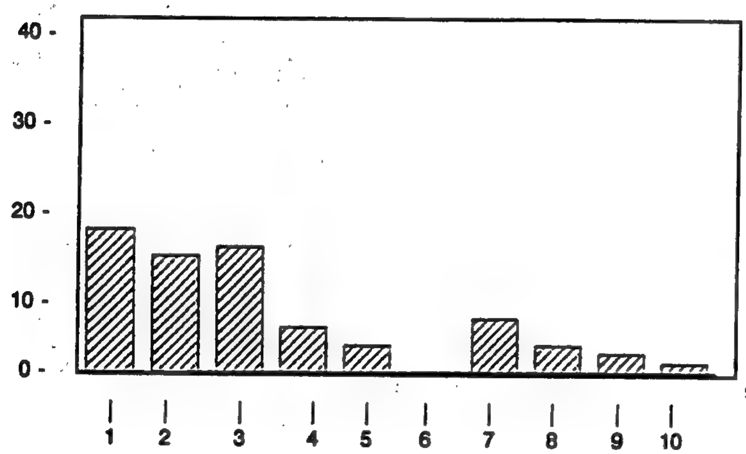


1. The necessity for research is felt by our company, and because of this, the preparation of a domestic joint research system with the universities and national research institutes is indispensable.
2. The necessity for research is felt by our company, and because of this, abundant and superior research personnel is indispensable.
3. The necessity for research is felt by our company, and because of this, it is indispensable to unify intra-company policies.
4. The necessity for research is felt by our company, and because of this, abundant research capital and complete research facilities are indispensable.
5. The necessity for research is felt by our company, and because of this, updating of a joint research system with public and private research organizations abroad is indispensable.
6. This is something that should belong to the nature of universities and national research institutes, and we do not feel the necessity of research in our company at all.
7. The necessity for research is vaguely felt in our company, but the specific research topics and directions are not clear.
8. This should be promoted as a large scale National project, and individual businesses, including our own company, are not at a stage to advance research independently.
9. The necessity for research is felt by our company, and because of this, updating of a joint research system with other domestic businesses is indispensable.
10. Other

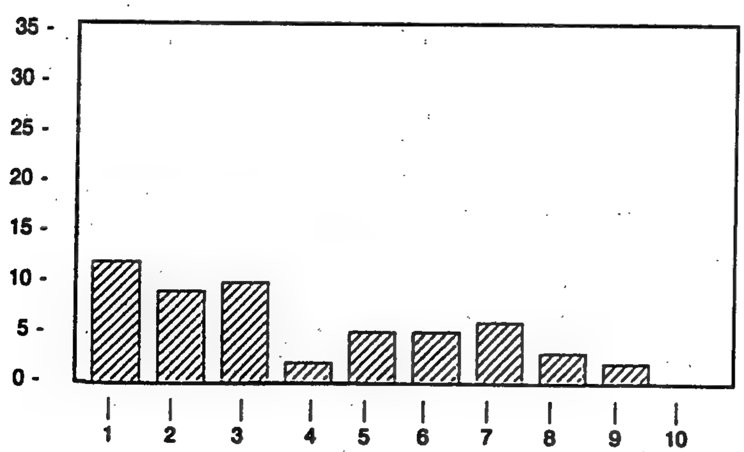
Chemical Products



Food Products



Other



1. The necessity for research is felt by our company, and because of this, updating of a domestic joint research system with the universities and national research institutes is indispensable.
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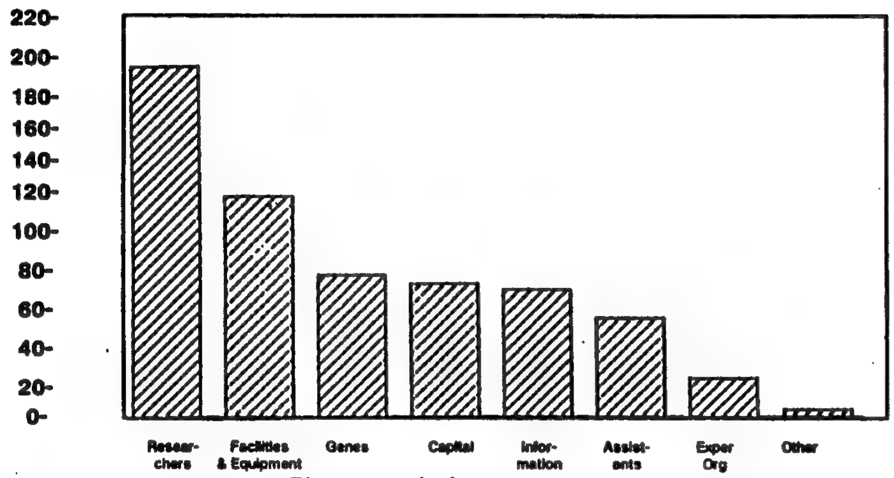
9. The necessity for research is felt by our company, and because of this, updating of a joint research system with other domestic businesses is indispensable.
10. Other

FIGURE III-8 THE FOUNDATION NEEDED FOR RESEARCH & DEVELOPMENT

Overall



Researchers: Full complement and guarantee of researchers

Facilities & Equipment: Installation and completion of research facilities and equipment

Genes: Guarantee of available genetic resources

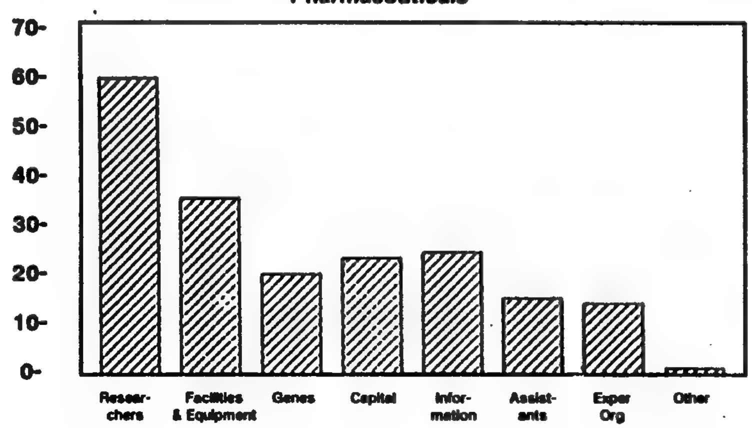
Capital: Guarantee of research capital

Information: Provision and completion of scientific research information.

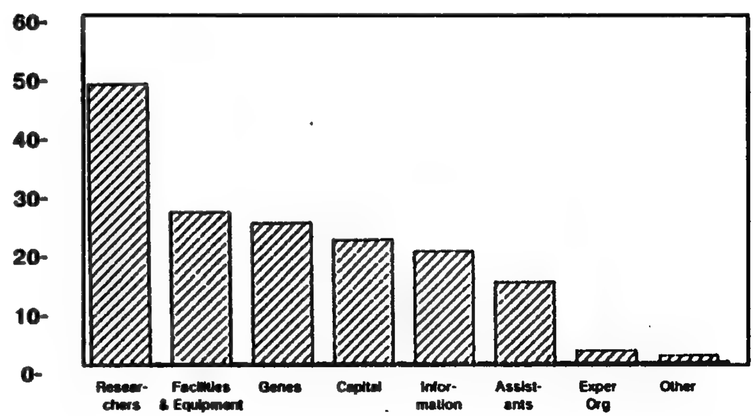
Assistants: Full complement and guarantee of research assistants

Experimental Organisms: Guarantee of experimental organisms and animals (Exper Org)

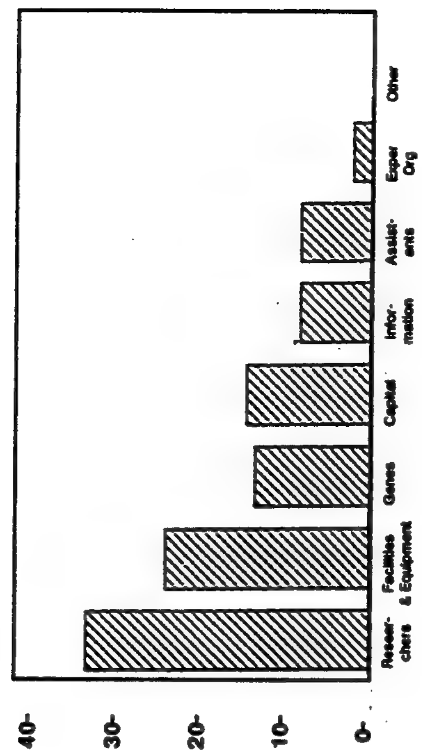
Pharmaceuticals



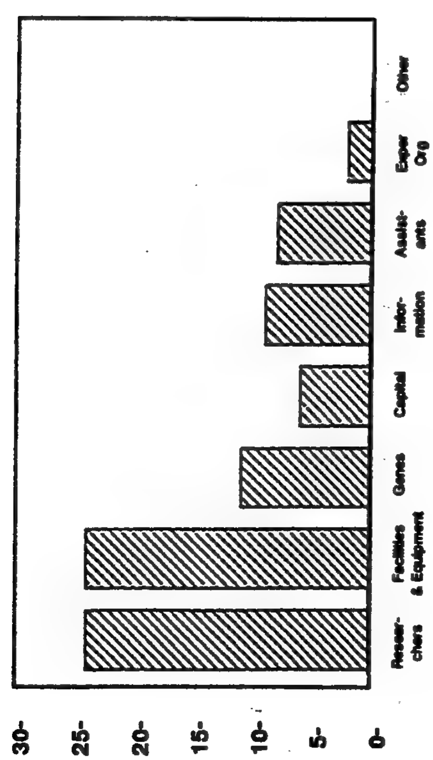
Agriculture, Forestry & Fisheries



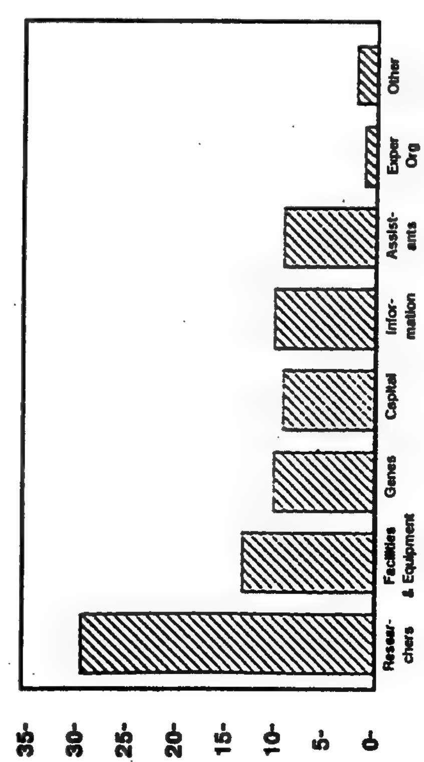
Food Products



Chemical Products



Other



In addition, following these items came "an insufficiency of research personnel." Concern for "quantity" of research personnel greatly outstripped concern for "quality" ("the quality of research personnel is still low").

The problem of research personnel was also indicated in another question concerning "the research and development base considered necessary for the future," and the results are shown in Figure III-8. The most frequent response was "completion and a guarantee of researchers" (about 90% of respondents cited this, and in food and related fields nearly all members gave this response). This was followed in order by "preparations of a full compliment of facilities and machinery for research," "a guarantee of effective genetic resources," "a guarantee of capital for research," and "preparation of complete scientific and technical information." Moreover, although the total number was small, there was a greater tendency for the pharmaceutical field to answer "a guarantee of experimental animals, etc."

Meanwhile, in order to grasp the present qualitative conditions of research personnel, the questionnaire asked about the structure of the academic backgrounds of the researchers. The results indicated that about 40% of the entire personnel were graduate school graduates (doctorate courses and masters courses), and approximately 40% of the remainder college graduates (refer to Figure III-9). When looking at the various fields involved, the pharmaceutical field in particular showed a greater tendency than others to have a high percentage of highly educated personnel. Here, the percentage of graduate school graduates exceeds 50%. In contrast, the fields of agriculture, forestry and fisheries and the food products field displayed a tendency to have a somewhat lower percentage of graduate school graduates. In a survey conducted by the Ministry of Agriculture, Forestry and Fisheries related to policies addressing to the quality of research personnel and personnel training, it was found that currently the most common means to handle this is with in-house training. The trend in future planning, however, indicates the intention to dispatch personnel to other domestic and foreign organizations for training (refer to Figure III-10).

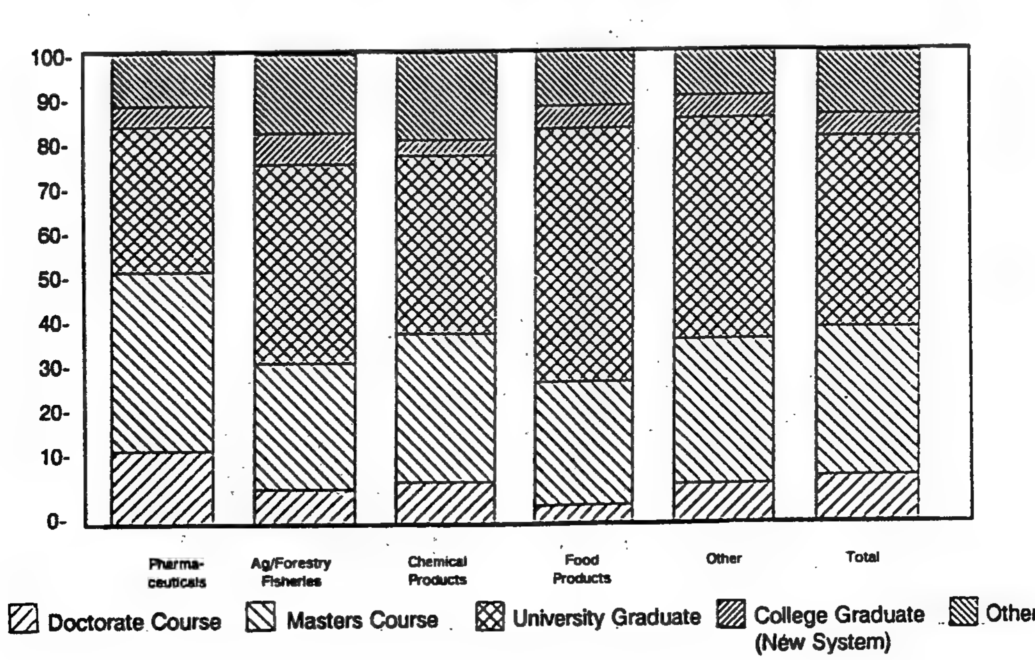
The items cited above gathered 30% or more of the total responses. Besides these, the items which received the most responses and the characteristics of the fields in relation to them are, in order of frequency, "marketability is unknown," "the quality of research personnel is low," and "effective genetic resources are few or unknown."

Among these, there was a tendency for a higher percentage of responses from the fields of agriculture, forestry and fisheries and from the chemical field to answer "available genetic materials are few or unknown." More or less related to this, the questionnaire asked about the "subjects" and "places" of future research materials (bio-resources), and these results are shown in Figures III-11, III-12, respectively.

Likewise, compared to other fields, the field of food products showed a tendency for a higher percentage of "public acceptance has not been built up," "a regulatory

FIGURE III-9 COMPOSITION OF THE ACADEMIC BACKGROUND OF RESEARCHERS IN POSITIONS OF MANAGEMENT AND RESPONSIBILITY

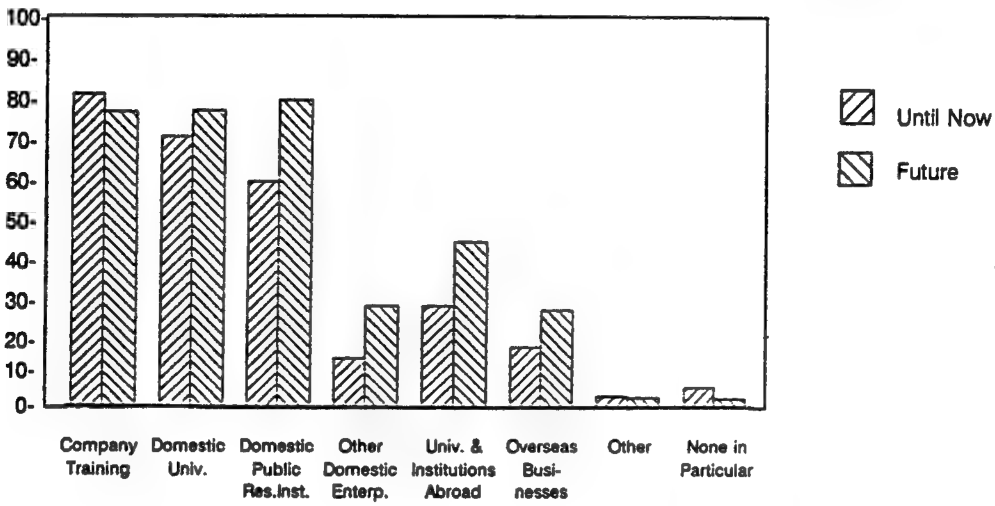
(%)



system and framework for safety has not been established." In addition to these two items, "the regulatory system and framework for safety is too strict," was often cited, and it could probably be said that although these more or less differ in substance, the percentage of total responses (in all fields) is high regarding to "safety related problems."

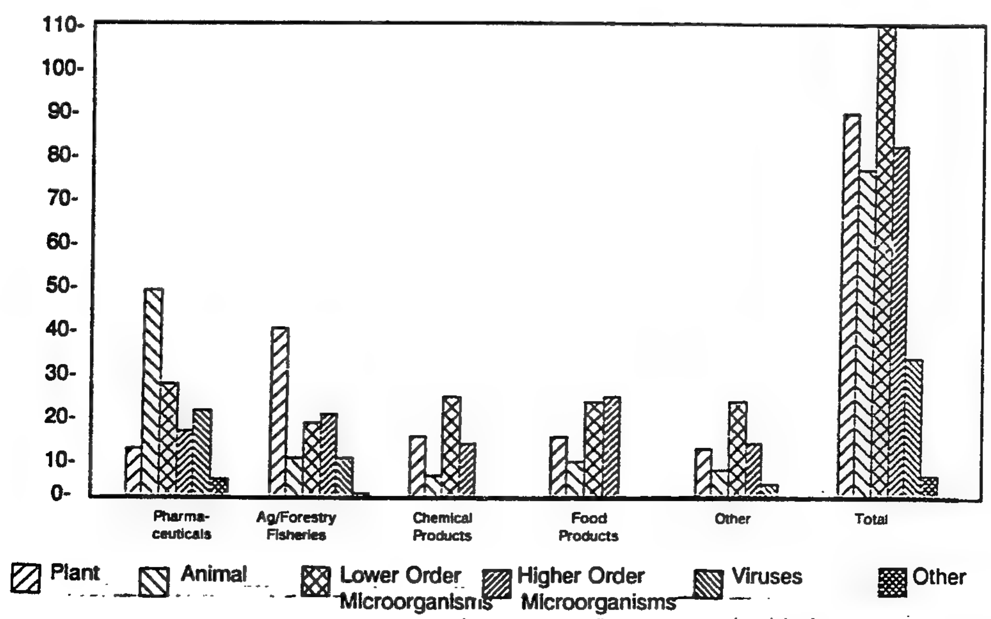
On the other hand, in the results of the interview survey (opinions concerning the practical application of biotechnology) that will be described later and in the free response section of the questionnaire, "a cooperative system between industry, academia and government" was cited relatively often as something that will be increasingly necessary in the future. In the responses to this question (question 5—future problems in the practical application of biotechnology), however, few responses indicated that this is thought to be a problem (or an obstacle) or that "it is insufficient." In addition, research managers of private enterprises were asked what their "expectations" for a system of cooperation

FIGURE III-10. PERSONNEL TRAINING POLICIES OF PRIVATE ENTERPRISES
(%)



SOURCE: "Urban and Rural Prefectures: Biotechnology Research & Development in Private Enterprise" (Industry of Agriculture, Forestry & Fisheries)

FIGURE III-11 FUTURE RESEARCH MATERIALS
(BIO-RESOURCES)



between industry, academia and government may be, and what "items they see as necessary for future advancement." The results of these are indicated in Figures III-13, III-14, respectively.

First, the most frequently cited expectation was "personnel training," and this was followed by "a gathering and exchange of all kinds of information," "a division of responsibilities in the field of fundamental research," "effective utilization of facilities and equipment for research," and "the formation of a personal network between researchers." Likewise, about 40% of the responses regarding areas considered necessary for future advancement indicated "simplification of business procedures" and "clarification of the treatment of research achievements." About 30% of the responses indicated "expanding the degree of freedom in research themes," "public disclosure of information relating to the system and arrangements for the exchange of research, etc.," "expanding the scale of capital output," and "greater public access to research facilities and equipment."

Finally, for reference purposes, the principal responses to the free answer questions concerning "the special characteristics or distinctive features of the biotechnology" field are enumerated below.

- It requires a vast amount of capital and an extended research period in order to obtain a practical application. It is extremely difficult to set goals in relation to the risks this incurs and the investment it requires.
- Fundamental research and applied research are extremely close, and it is easy to make practical applications immediately after success in fundamental research.
- It is extremely important to accumulate fundamental research relating to the phenomena of life and the functions of living organisms. Under the current circumstances, this has not yet been sufficient.
- When looking at the earth and at the natural world, it is necessary to have a consensus concerning the coexistence of biotechnology and humankind.
- It is necessary to have a collaboration with and a system of cooperation between industry, academia, and government as well as a network between them.
- It is necessary to develop new methodologies and technologies.

(2) The Thinking of Businesses in Relation to the Practical Application of Biotechnology

In the survey concerning the example of practical applications that were cited in Section 2 of Chapter III, the survey subjects who were interviewed at that time were asked their opinions concerning the practical applications of biotechnology as it impacts their own field of research.

FIGURE III-12 FUTURE RESEARCH MATERIALS (PLACE)

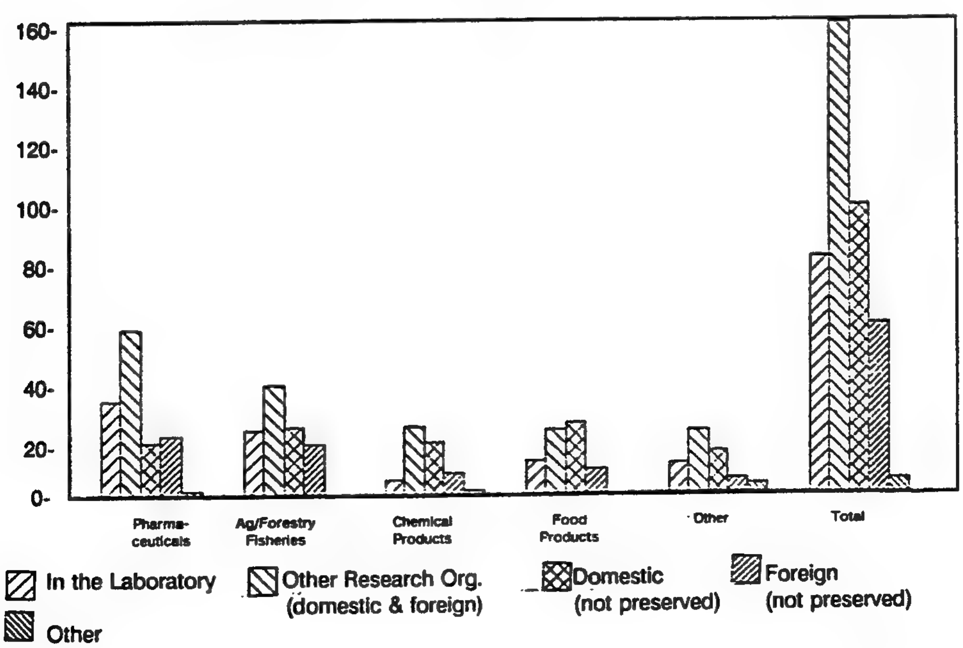
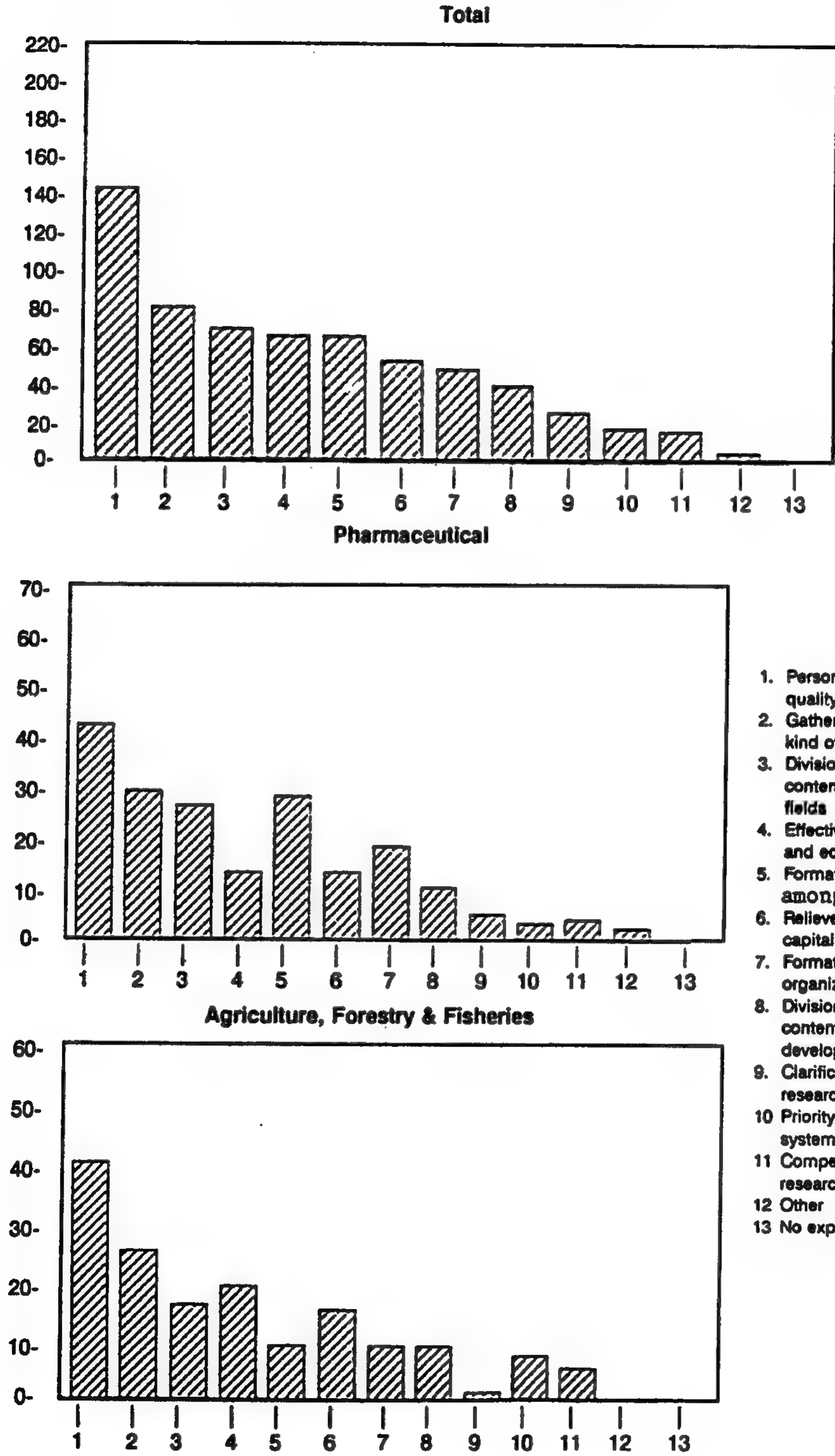
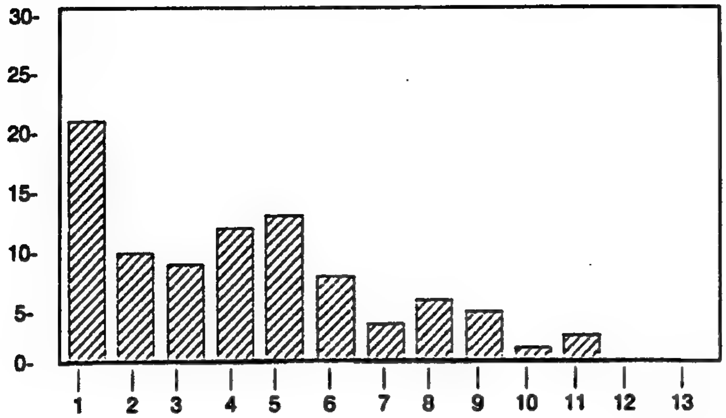


FIGURE III-13 EXPECTATIONS FOR COOPERATION BETWEEN INDUSTRY, ACADEMIA AND GOVERNMENT

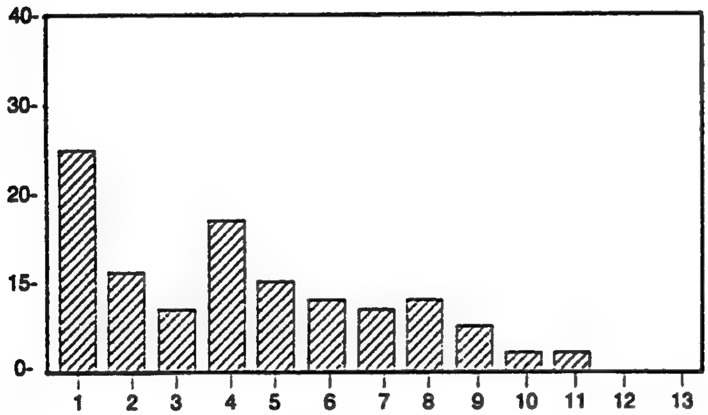


1. Personnel training (improve the quality of researchers)
2. Gathering and exchange of every kind of information
3. Division of the roles of research content in particular fundamental fields
4. Effective use of research facilities and equipment
5. Formation of a personal network among researchers
6. Relieve the burden of research capital
7. Formation of a network among all organizations with research organs
8. Division of the roles of research content in particular application and development fields
9. Clarification of the positioning of research themes
10 Priority treatment under the tax system
11 Competitive stimulus in respect to research contents
12 Other
13 No expectations in particular

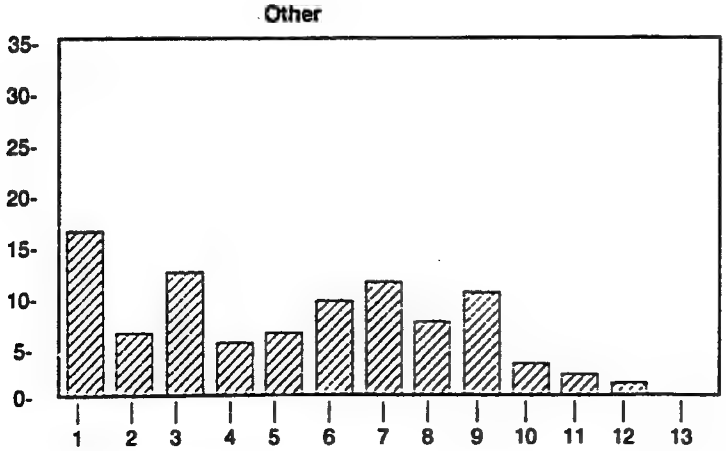
Chemical Products



Food Products

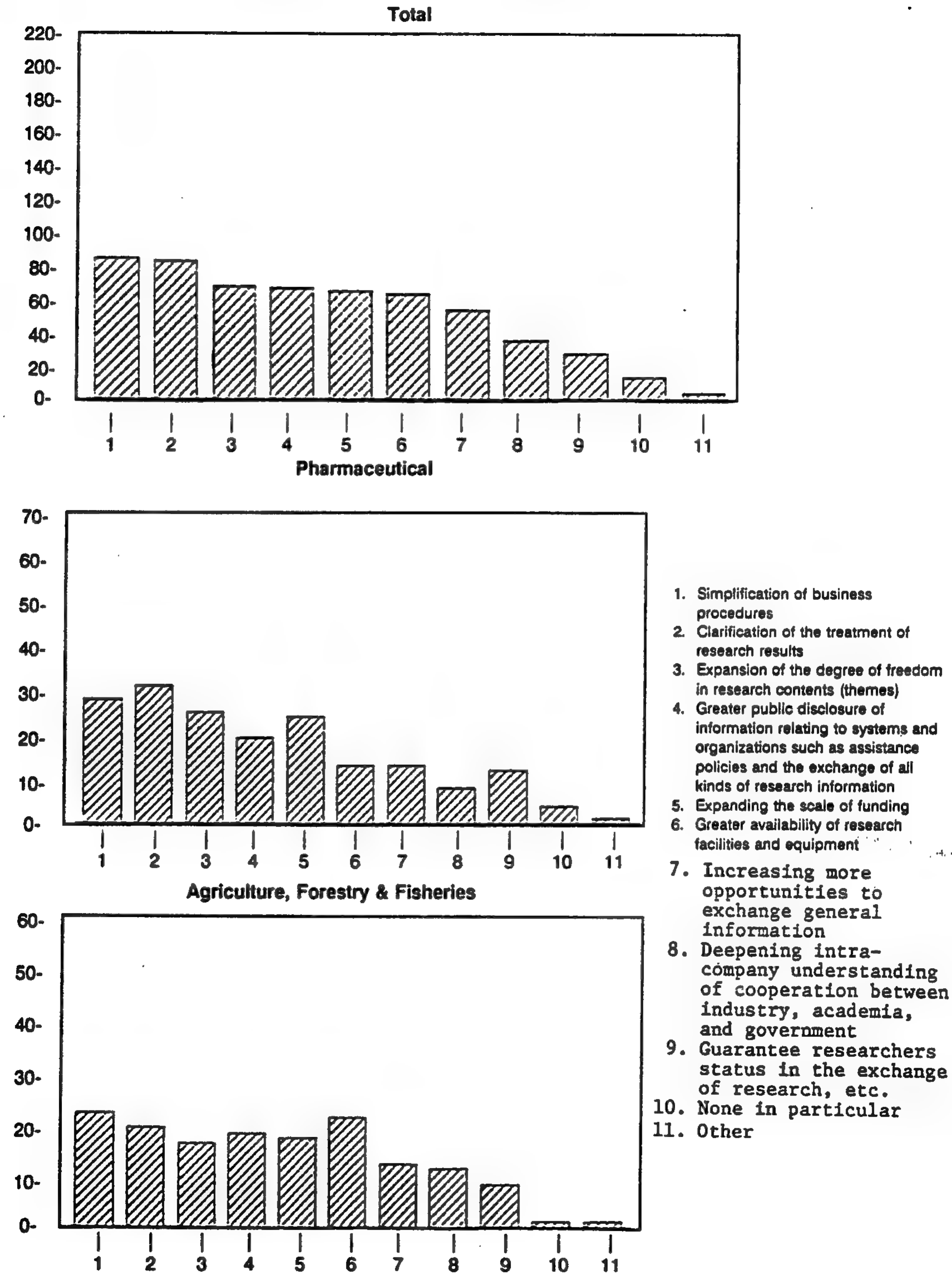


Other

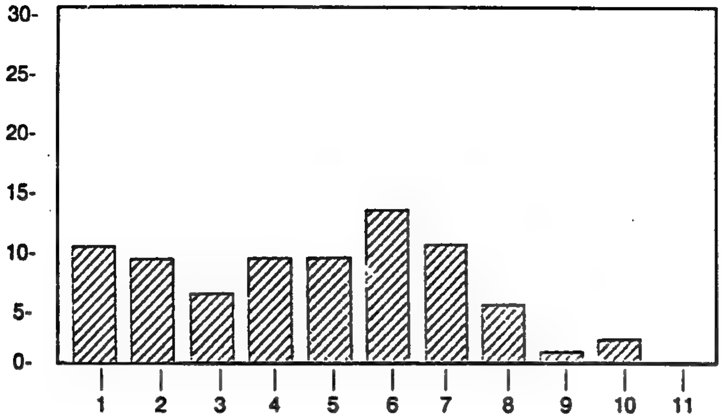


1. Personnel training (improve the quality of researchers)
2. Gathering and exchange of every kind of information
3. Division of the roles of research content in particular fundamental fields
4. Effective use of research facilities and equipment
5. Formation of a personal network among researchers
6. Relieve the burden of research capital
7. Formation of a network among all organizations with research organs
8. Division of the roles of research content in particular application and development fields
9. Clarification of the positioning of research themes
10 Priority treatment under the tax system
11 Competitive stimulus in respect to research contents
12 Other
13 No expectations in particular

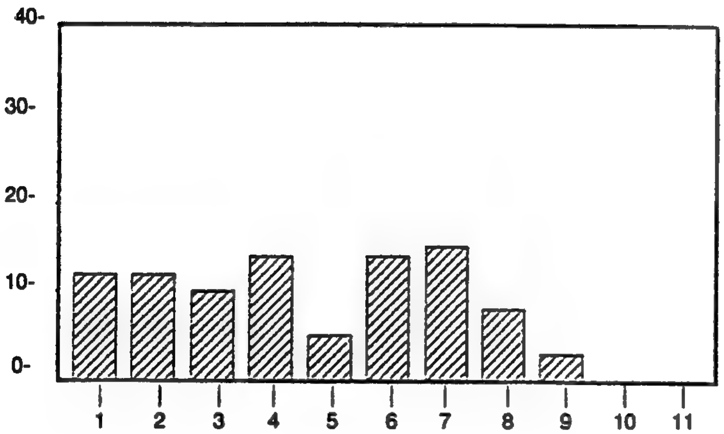
FIGURE III-14 FACTORS NECESSARY FOR THE COOPERATION BETWEEN INDUSTRY, ACADEMIA AND GOVERNMENT



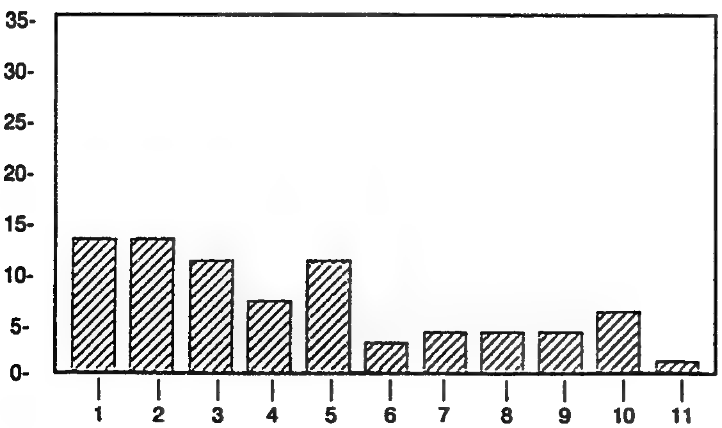
Chemical Products



Food Products



Other



1. Simplification of business procedures
2. Clarification of the treatment of research results
3. Expansion of the degree of freedom in research contents (themes)
4. Greater public disclosure of information relating to systems and organizations such as assistance policies and the exchange of all kinds of research information
5. Expanding the scale of funding
6. Greater availability of research facilities and equipment
7. Increasing more opportunities to exchange information
8. Deepening intra-company understanding of cooperation between industry, academia, and government
9. Guarantee researchers status in the exchange of research, etc.
10. None in particular
11. Other

These results are arranged as follows:

- When considering the use of things produced by living organisms, the development of applications is still not very advanced. We have not come close to fully exhausting the possibilities of the vast variety of substances that are produced from living organisms. Because of this, it is important to have many systems of evaluation (or to establish these), and it is necessary to gain a deeper understanding of living organisms. Moreover, the exchange between differing industries is also linked to the discovery of new uses.
- The so-called downstream technologies such as separation, recovery, and refining technologies are important. The development of new technologies for these, and the effective utilization of existing technologies (or the interdisciplinary areas linking these with basic biotechnology) are not yet sufficient.
- It is necessary to promote fundamental research (in view of "the ideal forms and properties that living organisms have," "learning from nature"). In addition, fundamental research must also take into consideration intellectual property rights such as patents, etc.
- Future collaboration with academia and government is important. It is anticipated that in areas which business finds it difficult to conduct fundamental research, research will be advanced in conjunction with academia and government, that more doors will be opened, and that places for joint interdisciplinary research will be established.
- Furthermore, it is necessary to specify the role and responsibilities that range across all those involved in order to make best use of respective characteristics and abilities of each. A system to deal with the results, etc. related to this cooperation must be perfected.
- In order to make practical applications it is necessary to combine specialized technology from every industrial field, but a plan to smoothly bring this about has not yet appeared. Because of this, there are many instances in which the fruits of the respective research technologies stand idle. Additionally, it is felt that even in academic associations, it is necessary to have a system which can link data structures horizontally.
- Because technology is advancing rapidly, it is hard for the general public to understand. Public relations activity to build up public acceptance is insufficient. Besides the efforts of business, a consistent national system including education is necessary.
- Astute administrative responses are needed in relation to the rapid advance of technology in every system. Moreover, there is a particular need for international harmonization in regard to patents and safety, etc. To this end, it is hoped that we can consistently keep up with the technical information from the administration and with overseas trends.
- In undertaking research, the first decision is to stipulate firm goals. Although there may be changes, these goals start from "technology."
- Once a technological development succeeds, there is a tendency to concentrate attention on that. In the future it is important to have more creative research.
- There are times when the opening of a market—other than technical development—is a large factor (low marketability is a problem).
- Other: When considering the production of chemical products by biotechnology, costs in comparison to ordinary chemical processes become problematic. Because of this, the use of biotechnology cannot help but focus on areas where there is demand for special structures such as the omission of steps in a manufacturing process, or for optically active substances.

In food processing, the mainstream will be the development of new products by improving basic ingredients and manufacturing methods. It is also thought that biotechnology will have an important role in drawing out new properties and characteristics that materials and products have.

In contrast to chromatography, which measures many components simultaneously, the biosensor would develop in a direction that would bring out such special characteristics as "the ability to measure single components" and the "ability to measure substances which cannot be measured chemically." However, the market for these will be small. The establishment of stability and selectability are the important technical issues in this.

IV. Reflections on the Practical Applications of Biotechnology

1. The Special Characteristics of Biotechnology

The difference between biotechnology and other technologies stems from the fact that the focus is on living organisms. For example, it can be said in general that production by living organisms is usually characterized by a slow reaction time, that pure materials produce distinct substances, and so on. Throughout this questionnaire survey research, several features appear that should be called the characteristics of biotechnology in regard to its practical applications. These can be arranged as follows.

(1) Fundamental Research

One of the most striking characteristics of biotechnology to appear was that of "fundamental research." Biotechnology is something that takes "living organisms" as its starting point. Because of this, the most important issues from the standpoint of promoting research and development are: 1) how to explain the ideal functions and properties that these living organisms have and 2) how to discover new things within them. It is thought that the possibilities contained within living organisms is close to infinite; however almost nothing is known about their true conditions.

With this in the background, biotechnology is considered to have the following characteristics: 1) The results of fundamental research will be quickly and easily made

into practical applications, and 2) The boundaries between fundamental research and applied research are obscure.

In other words, biotechnology itself is a technology which generates "knowledge," and advances in research and development toward practical applications and advances in fundamentals will go hand-in-hand (both progress spontaneously and in parallel).

(2) Possibilities for Applications to Many Fields and for Uniting Many Fields

In the process of their life activity, living organisms produce and secrete many kinds and varieties of substances. These substances and their productive functions are expected to yield many uses as direct substance production technologies in many fields, especially with pharmaceutical and chemical products.

Moreover, by grasping the phenomena of life from the engineering point of view, the uses and imitations of these phenomena have the potential to change greatly conventional design concepts in such engineering fields as electronics, materials, and mechanics. For example, this is just what neuro-computers have done. In this way, biotechnology—other than being used as a direct material production technology as stated above—is a technology with the characteristic of being able to combine with (or to be incorporated into) technologies in many other fields.

Further, in order to make practical applications of biotechnology we feel that the needs and the necessary technical seeds exist or are latent in an extremely broad range of fields.

(3) Difficulties in Making Technical Forecasts

As described above, research and development in biotechnology greatly relies on the discovery of new functions of living organisms. Specifically, there are many cases in which the new seeds that have been opened up and have produced results as a consequence of study and research are directly linked to a particular new technology. Because of this, it is naturally difficult to make technical forecasts concerning biotechnology.

This often leads to the difficulty of setting goals in relationship to research and development in private enterprises.

(4) Other

Although this cannot be called a characteristic of biotechnology, one cannot help but feel that there are trends in "technology" (for example, there is the overreliance and adherence to already existing technologies such as genetic recombination technologies, etc.). Specifically, biotechnology itself is not something born exclusively out of industrial needs or out of the needs of the general public. Rather, it has had its start as a "technology" arising out of academic research, and it is those needs that draw attention, disseminate and popularize the technology.

Nevertheless, these circumstances infer that research goals are first set from the technology, and this is one contributing factor making it difficult to generate highly creative research results.

When considering the problems and the policies facing the application of biotechnology, due consideration should be given to the special characteristics of biotechnology outlined above. Consequently, we will build on these characteristics in the following as we consider the future problems and obstacles to be overcome in order to bring about practical applications of biotechnology. Now then, we will arrange these problems in the order of importance already indicated in the questionnaire and interview surveys.

2. Policies and Issues in the Practical Application of Biotechnology

(1) The Understanding of "Living Organisms" (the Completion and Strengthening of Fundamental Research)

It is vitally important to proceed toward the completion of fundamental research. In particular, we must return to the "living organism" which is the source, deepen our understanding of the living organism, and broadly disseminate that understanding.

If the structures and functions of living organisms are pursued from every angle and the data complied so that at some point in time this data can be construed as a single lineage, there would be very high potential for an epoch-making breakthrough in biotechnology. Moreover, it is extremely important to continue studying the new functions of living organisms (or the living organisms which have these) on into the future if only to reveal the many aspects that cannot be theoretically derived.

Following is a list of the items considered necessary to complete and strengthen this kind of fundamental research.

1) Cooperative Promotion To Bring Out the Relative Strengths of Industry, Academia, and Government

In recent years even "industry (private enterprise)" has heightened its recognition of fundamental research, and policies to strengthen this trend are being planned. Nevertheless, the fundamental research being conducted by industry is not necessarily the same in content, character, and conception as that in academia and government.

Specifically, research conducted by industry generally: a) is determined to a certain extent by objectives and goals (products, etc.); and b) is of a type that searches the seeds rather than search for scientific theory. In contrast to this, the special features of the academic approach are: a) greater weight is given to the pursuit of scientific theory;

and b) long-term research is conducted. In addition to these, the fact that academic researchers are younger is probably also a characteristic. Finally, in a certain sense, government research is characterized by an intermediate position to these two.

Now then, it is necessary to fully activate what could be called the special strengths of each of these. Specific studies relating to individual cases concerning the division of roles and responsibilities for industry, academia, and government need to be fully undertaken in the future.

2) Long-Term Vision and Thinking

In a certain sense, biotechnology has as its object the black box of what is called the living organism. To explain the functions, etc. of living organisms it is necessary to adopt a long-term vision in tracing lineages and in pursuing new functions.

Thus, research of the fundamental kind is not necessarily something that is advanced only by having high level technology at one's beck and call. One must not ignore the building of a base of information by the long term compilation of groundwork efforts ("pick and shovel research").

Certainly this is so with academia. Conducting this kind of research in private enterprise, however, is thought to be rather difficult, but at least this long term viewpoint and way of thinking should be understood.

3) Securing and Training High Quality Research Personnel

Securing research personnel is a big issue in the completion of fundamental research. The fact that in the results of this questionnaire survey, there were more responses given in relation to quantity than to quality, speaks of the importance and urgency of this particular problem. Certainly, it should just be assumed that there is a problem with the quantity of research personnel, but when it comes to fundamental research, great weight should also be given to the qualitative side.

In the future it will probably be necessary to implement a policy that nurtures and guarantees this qualitative aspect of personnel. (In the questionnaire there were many responses that expected the training of personnel through a cooperative system of industry, academia, and government.)

4) Basic Preparations To Have Joint Ownership of the Advances and Results of Research

A research and development base is also an important factor in order to promote research.

When looking at the financial aspect, basic research into biotechnology is characterized by long-term research. While it is highly important to have research that may not easily proceed from theory in its exploration of new seeds, the attendant risks are rather high. Because of this, we are seeking to build a support and aid system to advance research which would take into account this financial aspect.

In addition, it is also important to deal with joint properties (or build a base for this purpose) in relation not only to the promotion of research, but also in relation to the specific positioning of the results obtained and the resources discovered by fundamental research within the total wealth of biotechnology.

First, one policy for this is the preparation and completion of a data bank. It is assumed that a policy promoting a shorter time and a greater convenience in the systematic upgrading and access of information will also be important in the future.

Moreover, by positioning a so-called gene bank to perform the same roles, it is expected that a system of preservation and distribution will be completed (at present, many transfers of genetic resources occur via links between individuals), that genetic resource information will be upgraded, and that mutual networking and cooperation will be perfected.

In addition, other fundamental aspects of joint ownership would include the promotion of regulations and standards (for example, setting standards and regulations for bioproducts) and the repetition and storage of fundamental experimental data for this.

(2) The Development of a Total Production Technology

Next, in order to consolidate the knowledge learned from living organisms and to perfect it (i.e., make practical applications) in a final form, it is important to build up the basic technologies of biotechnology, i.e., genetic recombination, cell fusion technology, etc. It is important also to construct a complete system of production technology that includes peripheral technologies and other related production technologies that lead all the way to the final target product. In the questionnaire and interview surveys the necessity to combine biotechnology with already existing technology and processes into a system of productive technology was indicated time and again. It is also necessary to develop new processing technologies, in particular, the separation, refining and recovery technologies that support the basic technologies such as genetic recombination, etc. which deal directly with the living organism.

In the specific examples of practical applications that have been cited, these support technologies and related production technologies have been undergoing technical accumulation and have always been standing in the background. We have seen several cases where they were directly linked to practical applications.

Specifically, it is important to simultaneously and in parallel advance the development of each technology which is something other than a fundamental biotechnology directly dealing with living organisms. It is also important to develop technologies in mediating fields

that link biotechnology with other technologies, and to build up a total and complete system (or to take up research and development from this point of view). Development in this area of technology has an intimate connection with the development of biotechnology as a whole.

(3) Discovering and Connecting the Wide Range of Existing or Latent Technical Seeds and Needs

A case has been made in section (2) above for constructing a system. An important key to the success in developing practical applications of biotechnology lies in discovering and making the connections between the technologies (or their seeds) and the research results which exist in each industry, field, or organization. In particular, due to the very nature of biotechnology, these technologies and their seeds span an extremely wide range, and currently a large portion of them is not being fully utilized.

The same things said about technical seeds can also be said about needs. The needs embraced by industry, academia, and government naturally differ, and there are also differences between the needs of different kinds of industries. In the current state of affairs, these are not precisely understood, and it is very important to discover these and make the connections.

Moreover, having technology and seeds is one thing and having needs is quite another. Perhaps many achievements will be accomplished between the two if there is an exchange between seeds and needs.

In order to discover and effectively utilize the latent possibilities in these other industries and fields, it is important to create a network which includes general information, technical information in particular. Along with this, in order to fully study their benefits and uses, it is important not only to position the antennas toward the outside, but to open the eyes to property already possessed such as genetic resources and technology (not limited to biotechnology) that has been established on its own in the past. Another key point here is to have the capacity to evaluate these for combined purposes (or to establish and introduce a system of evaluation for this).

The discovery and exchange of seeds and needs are intimately linked. As greater weight is given this in the future, exchanges between differing industries and between industry, academia, and government will increase. The following is a list of items relating to the advancement of this exchange that we consider important for the future.

1) Determining the Place for Exchange

First, it is fundamental to set up a "place for exchange (a system)." Exchange between different industrial categories and exchange between industry, academia, and government is already being promoted and incorporated into specific policies, not just for biotechnology, but for all kinds of joint research systems. In the future they will seek to establish biotechnology in particular as the place for a broad range of exchange that is not confined to closely related industries and fields.

2) The Completion of Outlets and Mediating Organizations (Functions)

In order to make full use of exchange systems (organizations) and to activate exchange among areas outside what has been organized by policy, it is necessary to establish organizations (functions) to act as outlets and to provide mediation. The primary role would be the dissemination information (the exchange of needs, etc.). For example, in private enterprise the first contact (the opportunity for exchange) with other organizations often has been personal contacts or the academic conference fulfilling this role. This kind of contact is inherently limited in scope, and there are very good chances that the areas of concern for each do not exactly coincide. When looking at the present situation, there is great demand for an organization (function) that can fulfill the roles of collecting, consolidating and presenting specific needs for exchange of research on biotechnology (for example, whether or not there is a desire for exchange, specific research contents, expectations in relation to the division of capital, the exchange of personnel, and procedures in relation to exchange, etc.).

Moreover, other roles that mediating organizations should take on would be support activities for outlets, etc. fundamentally related to capital and facilities.

3) PR for Policies

In connection with 2) above, contact made by private enterprise with the government ministries and agencies responsible for policy is inevitably limited by the industrial categories and research fields used in the past. When considering the broad distribution of seeds and needs previously described, it is important to have wide ranging PR activities in relation to each aspect of related policies. This will provide opportunities for exchange between related organizations. (Needs relating to the availability of this kind of information also ranked high in the questionnaire.)

4) The Establishment of Accompanying Systems

Then again, accompanying systems and regulations must be prepared to match the promotion of exchange between industry, academia and government. If preparations are not made for this, there is the danger that the system will not fully function when obstacles to the free exchange between industry, academia, and government come about, or when occasions arise in which it is difficult to promote advanced research between them, even if there is a means for exchange.

One example would be the need for personal assurances to researchers during an exchange of personnel. Besides such manifest issues as salary, it is necessary to address treatment which does not readily meet the eye and to guarantee a free exchange.

Furthermore, it will be necessary to fully study the simplification of business procedures and the treatment of research results. These concerns occupied the highest positions among the responses in the questionnaire.

(4) Coexistence With Society and Humanity

When considering the influence exerted on society and humanity by science and technology, it is a fundamental imperative to plan for their coexistence. This issue holds great significance in the bare fact that biotechnology has "the living organism" as its object.

Representative of this problem is public acceptance. However, in the results of this questionnaire survey it cannot necessarily be said that a great many research managers directly cited public acceptance itself as an issue. In a certain sense, this is nothing more than the flip side of the immaturity on the part of biotechnology. (Put another way, this is a good opportunity to fully study this issue.)

When considering the examples in Europe and the United States of open air testing and the problems in building biotechnology-related research laboratories in Japan, it is anticipated that public acceptance will be an important factor when contemplating the practical application of biotechnology. 1) Along with biotechnology, science and technology as a whole is advancing rapidly. Because the interval between the development and the making of products has gradually shortened as technology has become more specialized, the contents of this technology is becoming ever harder for the average person to understand.

2) One vital concern for modern people is "health and safety." Indeed, "dietary conservatism" has become a force in the field of food production in particular.

3) In regard to 2) above, it is difficult to say that biotechnology is born only out of the needs of the average person. If the short term viewpoint is taken, biotechnology is not necessarily limited to granting direct benefits to the average person in the current time of material plenty.

From the above, there is concern for the possibility that, if this problem is overlooked, the achievements of biotechnology that will be produced in the future may come to naught, and that the development of biotechnology may become linked to results obtained in a series of detours. Moreover, because this kind of problem is never something whose character is to be decided in the short term, in the future it will be necessary to make careful efforts to build a widespread and general consensus as a meeting ground for biotechnology and human kind.

For this reason, it is first necessary to do a complete study of the role of biotechnology from a long-term and widespread viewpoint. Naturally, this study should not be limited to the narrow range of industrial uses that was taken up as the focus of this survey study. Furthermore, public relation activities are also important in the sense of offering some kind of material for the general public when they consider this problem. One specific policy for public relations activities would be, for example, the widespread opening of research institutes that include private enterprise. By including an educational aspect, the foundations will be laid for a system which thoroughly takes up these issues as a nation.

(5) Other

Through this series of surveys, many issues have been raised in relation to future problems or policies. We will only touch upon them here.

First, we have indicated that in biotechnology research there is a tendency to focus on the achievements, technologies (or that which surrounds them) which have already been developed. In the future it will be important to have more creative research, and in this, it will be indispensable to develop new research methods and methodologies.

Moreover, we have more or less taken up the issue of fundamental research in this chapter. It also is extremely important to prepare a foundation for research and development (including genetic resources). The fundamental direction for this has already been taken up in the "Report on Question #16 'A Fundamental Policy to Improve the Foundations for the Advancement of Science and Technology'" issued in December of 1989.

Additionally, if the entire area of practical applications is considered and not just the aspect of technical development, one cannot ignore the problem of the market. There are aspects to the marketability of biotechnologically produced products that are difficult to grasp. It is important to jointly promote the opening and security of markets in the sense of making complete use of the achievements of research and development.

Meanwhile, from another perspective, the administrative response to regulations and systems (rights related, safety related, etc.) is also an issue that greatly concerns the future development of biotechnology. For example, as the current upgrade, the completion of safety regulations and policies will be a big factor in the previously described problem of public acceptance. In terms of systems, there are the great questions of how adroitly we can keep up with the future trends in biotechnology (scientific technology) that are developing so rapidly and of how we can plan for international harmonization when at present international competition is intensifying.

Reference

Survey Report: The Present State of Genetic Resources

(Guest Researcher, K. Kumagai)

1. The Preservation of Genetic Resources

(1) Preservation Conditions

1) Changes in the Survey on Preservation Conditions

There is widespread recognition of the importance of the epoch-making developments in the life sciences, of the extraordinary developments in biotechnology research and development, and of the need to secure the bio-resources which provide the foundation for this. Concern regarding genetic resources is heightening, and in the course of conducting this systematic and comprehensive survey on the preservation of these resources, the actual conditions have gradually come to light.

Recently, while taking positive steps toward the quantitative expansion of the number of varieties and samples preserved, all agencies possessing genetic resources have also concentrated their energies on the improvement of such information as the origins and characteristics, the use values, and the conditions for preservation, etc. This information has been collated and published in preservation catalogues, etc. Because there have been efforts to create an environment in which these are easy to use and widely available, it is comparatively easy to grasp the current status of the genetic resources preserved in Japan.

The first link in the task of conducting a systematic survey of all the fields dealing with living organisms in order to learn the conditions under which Japan's genetic resources are preserved was the establishment of the Department of Life Sciences at the Institute of Physical and Chemical Research in 1974. The results of the survey are compiled in the "Survey Study Report on Systems for the Preservation of Varieties of Microorganisms and Experimental Plants" in March of 1975 by the Japan Science Foundation and the "Survey on the Actual Conditions of Experimental Animals and a Survey Study Report on General Systems for the Preservation of Varieties of Living Organisms" in July of 1975 by the Central Research Institute of Experimental Animals.

The earliest survey of plant genetic resources was conducted in 1972 by a research group participating in the International Biological Program (IBP), and the results were published in a report appearing in March 1975. Famous as a public reference in the field of experimental animals is the "Present Conditions in the Preservation of Species at National Universities" published by the Japan Society for the Promotion of Science under the supervision of the Ministry of Education.

Afterwards, preservation agencies and the number of specimens preserved of plants, animals, and microorganisms were assembled in the supplementary resources of the "Proposal to Secure Living Organism Resources for the Promotion of Bio-Science" conducted at an informal meeting of Bio-Science Committee Members in December of 1982 and in the supplementary materials for "Responses to the Question 'What policies are there to secure living organisms as genetic resources?'" presented in June of 1984. The time period of this latter survey is rather recent, but the range of agencies covered is very narrow and it has the quality of sample survey results.

Recent trends in surveys of preservation conditions include assembling more detailed information and organizing each field to correspond to the use objectives for the administrative divisions, for example, experimental organisms, seed culture materials, pharmaceutical plants, forest trees, and plant research materials. Specifically, in the area of experimental animals, there is the "Experimental Animal Species in National, Public, and Private Universities" (Revised in September 1985) assembled by the Research Center for the Preservation of Genetic Experimental Organisms of the National Research Institute of Genetics, and the "Catalog of Artificial Products and Genetic Resource Preservation at all National Universities" assembled by the Agriculture and Forestry Technology Center of Tsukuba University in 1985 and 1986. Surveys have also been conducted of forest species at all the forests experimentally run by Japan's universities, and there have been surveys of the actual conditions of preservation at botanical gardens.

In the field of gene and seed research materials for agriculture, forestry and fishery products, the center has been the Agriculture, Forestry and Fishery Gene Bank. This was designed in 1987 and 1988 to gather information not only from the agencies related to the Ministry of Agriculture, Forestry and Fisheries but also from research agencies in the urban and rural prefectures by promoting the creation and ongoing operation of a data base for genetic resource information. As part of its survey to determine policy for the preservation of resource organisms, the "Preparation, Study and Operation of Plant Genetic Resource Information" was advanced by the Science and Technology Agency. A survey of all national agencies was conducted in regard to the preservation conditions and the organization of information on plant genetic resources. The job of compiling this information was entrusted to the Agriculture, Forestry and Fisheries Technical Information Council, and the report, "Survey of Plant Genetic Resource Information Systems: Survey on the Actual State of Preservation Agencies," was drawn up in March of 1988.

Besides the above, detailed listings of the preservation conditions of Japan's genetic resources have appeared in the recently published "Collections of Plant Genetic Resources" (May 1989), and "Handbook of Resources"

(September 1989). These can be referred to for a summary of the number of preserved varieties and preserved specimens, the conditions of preservation, the methods of preservation and the preservation facilities.

2) Summary of the Number of Preserved Species and Preserved Varieties

a. Plants

The oldest data on plants appears in the Report of the Research Corps that participated in the IBP. This cites the results of a survey conducted in 1972. It targeted a total 104 organizations comprised of 37 universities, 28 national research institutions, 33 public research organizations and six private businesses. The total number of preserved items was 148 families, 499 genuses and 82,337 species.

In the survey study report on Systems for the Preservation of Species conducted by the Institute of Physical and Chemical Research in March of 1975, 23 representative preservation organizations were surveyed in regard to the number preserved items, the facilities for preservation, and the budget and personnel. For each organization the preservation goals, the characteristics of the preserved species, and the organisms whose varieties are considered important were indicated. While a detailed cataloguing of the number of preserved species was not conducted, several tens of thousands of species were cited in all.

In the supplementary materials to the Proposal to Secure Living Resources that appeared in December of 1982, there were 146,544 species and varieties of such agriculture crops as rice and wheat, 8,571 species and varieties and trees, 2,502 species and varieties of pharmaceutical plants, 403 varieties of other plants, and 46 varieties of seaweeds for a total of 158,066 species and varieties. This report emphasized that, in comparison to other advanced nations Japan is lagging behind in the number of preserved species.

According to the data from the National Institute of Genetics that surveyed varieties of experimental organisms (revised edition in September 1985), there were 88,989 varieties at 102 national universities, 1,599 varieties at nine public universities, 2,380 varieties at 13 private universities, and 266 varieties at one incorporated organization for a total of 93,234 varieties at 125 organizations. In the Catalogue of Crop Genetic Resource Preservation by Tsukuba University, there were nine species of minor grains with 1,139 varieties, seven species of beans with 5,194 varieties, 26 species of industrial crops with 1,876 varieties, 16 species of feed crops with 426 varieties, 24 species of vegetables with 1,212 varieties, 51 species of fruit trees with 1,715 varieties, 4,809 varieties of flowers and flowering trees (an estimated 100+ species) for a total of more than 200 species extended into 16,371 varieties. In the Index of Plant Genetic Resources, details are given about the number of preserved items classified according to crop and according to the university which preserves them. Information is given about the conditions of preservation for plant genetic resources in the national universities, etc. as well as about major grain types, minor grain types, types of beans and potatoes, types of artificial crops, vegetables, types of flowers and flowering trees, fruit trees, medicinal plants, etc. Using the two previously mentioned resources as basic data, subsequent changes have been added and corrections made. Many of the particulars are the same, and therefore we will omit them here.

The data cited in the Resource Handbook was current as of February 1987, and it brought together all the crop genetic resources that Japan preserves. It lists 47,680 types of rice, 57,297 types of wheat, 8,275 types of potatoes, 22,269 types of beans, 9,320 types of minor grains, 18,631 vegetables, 18,112 fruit trees, 15,071 artificial crops, 35,889 grass and feed crops, 23,703 flowers and flowering trees, 2,564 medicinal plants, 1,240 mushrooms, and 24,883 others for a total of 284,934. This total includes the forest species preserved by the Ministry of Agriculture, Forestry and Fisheries in the "Other" category, but it does not include the forest species preserved by universities, the plants preserved in botanical gardens, and the crops and medicinal plants kept by private enterprises.

Because the Survey of Current Preservation Organizations conducted by the Science and Technology Agency in 1987 attempted to grasp the current state of preservation by using a comparatively broad target range, we think that these results closely reflect the most recent conditions. Some 1,033 organizations were surveyed (317 universities, 428 public research organizations, 22 national research organizations, 75 botanical gardens, and 191 private enterprises). Subtracting the 255 organizations that did not respond, responses from 788 organizations were obtained. Among these, there was a total of 499 effective responses by these organizations. The totals for plant classifications were 151,329 edible crops, 11,891 industrial crops, 9,838 teas and mulberry varieties, 34,141 fodder and fertilizer crops, 20,240 fruit trees, 54,669 vegetables, 13,266 flowers, 19,141 flowering trees and greenery plants, 275 medicinal plants, 39,146 forest trees, 14,188 other experimental plants for a total of 368,124. However, some experimental forests, botanical gardens, herb gardens and research laboratories of private businesses were not included in this figure, and it is thought that the actual number of preserved species is much greater than this.

When looking at the above changes in the preservation of plant genetic materials in Japan, the numbers appear, at first glance, to have increased rapidly. However, this is in the main something that accompanies the expansion of the survey scale, and it does not accurately reflect changes in individual organizations. Nonetheless, when following the most recent changes in the number of preserved items, for example, seeds at the National Institute of Agrobiological Resources of the Ministry of Agriculture, Forestry and Fisheries, a clear increasing trend was seen with the growth from 34,025 to 35,793,

38,090, 42,791, 47,981, and 54,175 species from 1983 to 1988. Of course, it cannot be assumed that the same rate of growth in the number of preserved species applies to all domestic organizations, but with the effects of a variety of policies, it is certain that there is an increasing trend from year to year.

b. Animals

Actual survey reports concerning the current production and supply of experimental animals in Japan were published in 1973 and 1975. The surveys were conducted from the organizational viewpoint of promoting research into the life sciences. This was the first research study of preservation systems by the Central Research Institute of Experimental Animals. The report appeared in July of 1975, when an initial preparatory survey was conducted targeting 415 organizations. Some 243 organizations which maintain and breed animals for the purpose of preserving species and varieties were targeted for the main survey, and results were collated for the 222 responding organizations.

The survey results broadly categorize the animals that are maintained and preserved into mammals (this is further divided into gnawing mammals and other mammals), birds, amphibians and fish, and invertebrates. The number of organizations which support each animal is indicated. When the variety is known, the number of organizations maintaining each variety is also indicated. Following is a list of the number of organizations maintaining each kind of animal with the number of varieties shown in parentheses. There are: horses, 2; cows, 4; sheep, 3; goats, 3 (2); pigs, 4 (4); dogs, 17 (2); cats, 6 (3); rabbits, 31 (12); ferrets, 3; monkeys, 10; mice, 119 (311); rats, 89 (27); hamsters, 38 (4); guinea pigs, 19; rodents, 10; masutomisu [phonetic], 4; other gnawing types (19 types), 8; chickens, 9 (9); quail, 6 (12); geese, 1; frogs, 13; newts, 2; medaka, 3; goldfish, 1; crucian, 1; carp, 2; ayu, 1; shrimp, 2; oysters, 1; sea anemone, 1; jellyfish, 1; other marine animals, 4; drosophila, 6; silkworms, 1; mosquitoes, 1; cockroaches, 1; other insects, 2; parasites, 1; and protozoa, 3.

In the additional resources in the 1982 proposal, the mammals were divided into domestic animals and experimental animals. In the former there were 1,860 cows of seven kinds, 140 horses of four kinds, 650 pigs of four kinds, 104 goats of two kinds, 550 sheep of two kinds, 120 rabbits of two kinds. Of experimental animals, there were 2,200 monkeys of six kinds and varieties, one variety of dog, 22 varieties of guinea pigs, 434 varieties of mice, 62 varieties of rats, three varieties of hamsters, and 49 varieties of other experimental animals. Of birds, there were 116 types and varieties of chicken, 25 varieties of quail. There were 100 varieties of amphibious frogs; 30 varieties of the salmon family, 49 varieties of medaka, 17 varieties of carp, and 10 other varieties of fish; 1,172 varieties of silkworms, 1,918 varieties of drosophila, two kinds of honey bees, 1,500 cockroaches of two kinds, 123 varieties of flies and mosquitoes, 31,100 other harmful insects of eight kinds, 28 varieties of shell fish, one other arudemia [phonetic], and eight kinds of parasites.

Moreover, according to a survey of the varieties of experimental animals at a total of 336 related organizations by the National Institute of Genetics: of mammals, there was one variety each of horse, pig, goat and sheep, 17 varieties of rabbits, and seven varieties of dogs; of gnawing mammals, there were 1,097 varieties of mice, 245 varieties of rats, 58 varieties of hamsters, 25 varieties of guinea pigs, 66 varieties of rodents, two varieties of masutomisu [phonetic], and 33 other varieties of gnawing mammals; of birds, there were 68 types of chickens, 57 types of quails, 25 types of ducks; one variety of karugamo [phonetic]; of amphibians, there were 1,012 varieties of frogs, and six varieties of salamanders; of fish, there were 95 varieties of medaka, and 19 other varieties of carp; of shell fish, there were six varieties of ascidians, four varieties of oysters, and nine varieties of mud snails; of other aquatic creatures, there were 267 varieties hydra; of insects, there were 2,619 varieties of drosophila, 104 varieties of flies, 54 varieties of mosquitoes, 716 varieties of silkworms, four varieties of ants, and 30 other varieties of insects; five other varieties of nematodes, 185 varieties of protozoa, and one variety of parasite.

c. Microorganisms

In the results of the Survey Study of Variety Preservation Systems in 1975, at a total of 15 organizations that preserve nonpathogenic microorganisms there were 4,776 bacteria, 11,362 molds, 7,219 yeasts, 1,613 actinomycetes, and 24 phage. At a total of 16 organizations that preserve pathogenic microorganisms, there were 60,000 bacteria, 887 eumycetes, 110 actinomycetes, 214 viruses, 1,036 phage, four protozoa. At a total of 16 organizations that keep algae, there were 186 blue-green algae, 39 euglenophyta, 43 grey algae, six flame colored alage, 22 brown algae, 55 red algae, 507 axle algae, and 22 flagellar algae.

In the Additional Resources of the 1972 Proposal, of non-pathogenic microorganisms, there were 932 varieties of micro-zoa, 1,670 varieties of micro-phyta, 1,305 strains of phage, 11,157 strains of yeast, 14,405 strains of mold, 51,536 strains of bacteria, 5,281 strains of actinomycetes, 10,888 strains of viruses and phage; of pathogenic microorganisms, there were 4,472 strains of mold, 53,710 strains of bacteria, 107 strains of actinomycetes, 861 strains of viruses and phage.

According to a 1988 survey by the Japan Union for the Preservation of Microorganism Strains, at a total of 19 among the 24 organizations belonging to the union, there were 14,722 strains of filamentous cells, 11,905 strains of yeasts, 4,243 strains of actinomycetes, 90,789 strains of bacteria, 481 strains of viruses, 1,011 micro-seaweeds, six animal protozoa, and 21 protozoa. This did not include those microorganisms preserved by the Ministry of Agriculture, Forestry and Fisheries.

Furthermore, in the Survey of Varieties of Experimental Animals by the National Institute of Genetics, the total number of microorganism types maintained at 318 organizations such as the national universities was reported to be 204,838 strains.

Moreover, when looking at organizations that preserve microorganisms, the number of microorganism strains recorded at the Facility for the Preservation of Microorganism Varieties, Institute of Physical and Chemical Research, has increased yearly (from 600 to 1,000 strains per year), and the number of recorded strains at the end of the 1987 fiscal year was 6,138 strains (2,809 strains of bacteria, 1,545 strains of actinomycetes, 1,203 strains of yeasts, 581 strains of filamentous fungi). Further, the number of microorganism strains maintained in the Gene Bank of the Ministry of Agriculture, Forestry and Fisheries listed during the 1985 and 1988 fiscal years was 886 and 15,165 bacteria and actinomycetes, 720 and 13,252 filamentous fungi and yeasts, 60 and 1,209 viruses and phage, and eight and 1,887 others for totals of 1,674 and 31,513. This clearly demonstrates the recent tendency for the rapid increase in the number of maintained items.

d. Other

We have not touched on the others here, but there are organizations already using the latest advances in biotechnology to preserve genetic resources by tissue culture, cell culture as well as by gene level DNA preservation of such plant and animal tissues as pollen, ovula, spermatozoa and fertilized eggs.

3) Conditions of Preservation and Methods of Preservation

The methods for preserving genetic resources take on the forms that correspond to the characteristics of the living organisms. Hence, organisms may be maintained as a group to form an ecosystem, or as individual members, seeds, organs and tissues, germ cells, tissue and cell cultures, or DNA and RNA.

With plants, in order to maintain the genetic composition of the wild plants of a forest and its surroundings, the seeds are preserved in certain circumstances by providing protected regions and designated areas. In these cases, it is necessary to maintain not only the target plant, but the ecosystem that sustains it as well. As much as possible, it is necessary to avoid changing environmental factors that may destroy this balance, and it is necessary to allow the natural environment to affect any genetic or ecological changes in the plants.

Long lived trees and plants may be maintained by cultivating individuals in botanical gardens or nurseries. Plants at botanical gardens and herb gardens, and forest trees and flowering trees at arboretums are kept under artificially controlled conditions, but their management is much less involved than what goes on at nurseries that cultivate fruit trees, tea and mulberries. These latter have increased genetic control via artificial protection and selection. The nurture and propagation of herbaceous plants is accomplished by alternately culturing in a nursery and utilizing methods in an artificial environment to preserve a part of the plant body such as the root or stalk that is needed for the propagation of the next generation. With the improvements afforded by this latter method, the period in which the life span of the plant can be artificially maintained is lengthened, and this provides a means to shorten as much as possible cultivation within the nursery.

In order to preserve and propagate the species, it is the plant seed that plays the vital role in the maintenance and dispersion of life even under natural conditions. When seen from the standpoint of the preservation of genetic resources, seeds are also important for they are smaller than individual plants and have the advantage of supporting life while the surrounding conditions undergo change. Because the life span of most plant seeds can be extended in dry cool conditions, the preservation of genetic resources in the form of seeds is currently under rapid development. Low humidity, low temperature seed storage warehouses for this purpose are being built in all major countries around the world. In these, a large volume of seeds can be kept for a long period under stable conditions, and thus the viability of the seeds can be maintained. However, because some plant seeds, particularly aquatic plants and tropical plants, cannot endure drying, the long-term preservation of these seeds is perplexing, and the development of long-term preservation technologies for these kinds of seeds is pressing.

Even with woody plants, parts of the grain heads or roots can be maintained at low temperatures. This can be applied to the genetic resources of fruit trees, mulberries, tea, forest trees and flowering trees. More recently, it has become possible to preserve minute bits of plants through cultures. Buds, stems and leaves can be cultured in test-tubes, and by properly planting them, they can be maintained for long periods of time.

Pollen can be maintained for long periods by vacuum drying and keeping tightly sealed at low temperatures. This is being applied to fruit trees, etc. as a method for preserving compact resources that are genetically stable, and highly transportable.

Besides this, recent advances and progress in culture technologies have made it possible to preserve genetic resources by extracting the callus, culturing tissues and cells, and by freezing DNA fragments.

As with plants, animal genetic resources are being preserved in forms from groups to individuals, germ cells, culture cells and DNA. In particular, spermatozoa and eggs can now be preserved by freezing, and some established strains are actually being maintained by cell culture and by DNA level preservation.

Because they are so small, when microorganisms are being preserved, hardly any of the preservational form problems connected with plants and animals arise.

Because there are so many varieties to preserve, preservation methods appropriate to each kind are being developed. If there are many microorganisms to be preserved, they are preserved as isolated strains, and at times they will be preserved according to their use objectives, be that on the cellular level, or as virus particles, plasmids, DNA, or RNA, etc.

(2) Preservation Technologies

1) Significance of the Development of Preservation Technologies

The purpose of preserving genetic resources is long term stable maintenance with as little distortion of the genetic composition of the living organism type as possible. Another objective is to be able to effectively use and apply targeted genes whenever it becomes necessary. In order to be able to do this, the development of preservation technologies is indispensable. Because the genes which govern the form and substance of living organisms manifest information via the base strands which compose DNA and these are preserved and passed on by the living organisms that harbor them, the development of preservation technologies for living organism types is a fundamental imperative if we are to maintain the life of living organisms.

2) Preservation Technologies For Plant Genetic Resources

When attempting to support and preserve forest trees and wild plants as a group of individuals within a natural ecosystem, a protective zone is created by designating a specific area, and certain methods are employed to maintain and manage this. In this case, ecological observations are made as to what supports the ecosystem of this area, and a survey is conducted regarding the environmental factors. The goal is not to take positive actions to improve this area, but rather, the main task is to protect the area so that the present conditions may be supported. Thus, there is little room for technological participation here.

Long-lived plants that are maintained as individuals are grown under comparatively crude management at herb gardens, botanical gardens and arboretums, while fruit trees, mulberries and tea are cultivated in nurseries with such intensive management and support inputs as fertilizers and pesticides. Besides the common cultivation technologies applied to this latter category, there are also instances when such special cultivation techniques as dwarfing, crowding and potting are necessary. Because these kinds of specialized cultivation techniques require a large area and a large amount of labor and resources, it is important to minimize them and to develop techniques to conserve labor and resources.

The most widespread method for preserving seed propagating plants is to dry the seeds and store at low temperature and low humidity, and for many plants long term storage under these conditions is possible. The important area for technical development is the clarification of the factors and mechanisms influencing the loss of seed viability such as the harvesting of high viability seeds, drying methods, and storage conditions (temperature, humidity, containers, sealing methods, gas replacement, etc.). The goal is to establish storage conditions that organically combine these elements in a way appropriate to the maintenance of seed viability. It is known that the effectiveness of these conditions not only varies according to species of plant, but also according to varieties within the species. The ideal storage conditions for seeds would make exacting distinctions between each species and each variety. Another important element in technical development is keeping changes in the genetic composition of plants in storage to a minimum. Differences between genetic types in life span and differences in reaction to the storage conditions greatly influence mutations in the genetic composition of seed groups in storage. Because the increasing tendency for a sudden change rate cannot be ignored, it is necessary to come to a technical understanding of this and to establish countermeasures. Recently, advances in low temperature biology have made the preservation of plants by freezing at ultra low temperatures possible, and this has led to high expectations for the practical application of long term, genetically stable seed storage technologies.

In addition, research advances into seed life spans are making it possible to estimate the life span of seeds in relation to the storage conditions. However, because there is no other way to directly confirm the viability of the infinitely varied individual lots of stored seeds than germination experiments and viability examinations, it is important to develop technologies to that end.

Because plants have the totipotency to easily regenerate the individual from a piece of tissue or organ, methods are being used to preserve plants while controlling the growth of a piece of organ or tissue. With long-lived woody plants, it is possible to preserve spearheads and roots at low temperatures, and the adaptation of this to fruit trees, mulberries, tea and some forest trees has been technically established as a method to ensure genetic stability while saving space and labor. In addition, strawberries, carnations, potatoes, and casabas have been preserved by subjecting shoot apex tissues to ultra low temperatures, and woody plants such as fruit trees, mulberries and tea have been preserved by culturing shoot apex tissues at normal temperatures and re-planting. Moreover, with plants that are nurtured and propagated like sweet potatoes and potatoes, small amounts of plant tissue can be preserved in test tubes. Growth can be regulated and the period for re-planting lengthened by adjusting such conditions as the culture medium and light. Not only does this save space and labor, but it is also an effective means for improving transportability and for preventing disease.

Preservation of pollen and ovules, the germ cells of plants, by vacuum drying and storing tightly sealed at low temperatures has been tested on fruit trees, etc., and it has received high marks as an applied technology for

preserving genetic resources that can be used to overcome discrepancies in flowering periods and geographical barriers. Besides these techniques, there have been far-reaching applications of culture technologies for preservation on the cellular level that have accompanied the recent advances in biotechnology such as the low temperature preservation of the callus, which has high growth capabilities, and the maintenance of cell clusters by subcultures. Further, there are even attempts to preserve single cell protoplasts at ultra low temperatures. However, with the callus and protoplast technologies, it is assumed that an individual can be easily redifferentiated at any time, yet genetic stability remains a sticking point both for these technologies and for subculture. More technical studies are needed.

Moreover, freeze preservation of genes on the DNA and RNA level is also being studied as an application of genetic manipulation technology, and the possibility of practical applications of this are being confirmed. The development of these technologies suggests the possibility of literally operating a gene bank with a DNA library. This goes hand in hand with the establishment of technologies to analyze the structure of genes and technologies to adjust DNA fragments that have specified base sequences. Thus, it is expected that genetic resource preservation technologies will have a great role to play in the future.

3) Methods To Preserve Animal Genetic Resources

With animals as well, there are all kinds of preservation forms from groups of individuals to the DNA level. The necessary preservation technologies vary for each level. In preserving most wild field animals and some marine animals as groups of individuals in natural ecosystems, resources are preserved and the genetic characteristics of the group are supported by providing a protected area and allowing free feeding and free movement in the wild. Positive human control is difficult both environmentally and genetically. However, the minimum necessary conditions to achieve the preservation goals must be satisfied. For example, the necessary numerical limits to the individuals existing in the natural environment must be set in order to ensure a fixed size to the biosphere and to support the group. Thus, many difficult problems remain to be worked out.

Insects and small animals such as domestic animals, poultry, some marine animals or experimental animals can be preserved in an artificial environment by feeding and nurture. These animals can be genetically controlled by breeding and chromosome manipulation, but the essential points vary in the technical development necessary for each species. The management of feeding and nurture requires extensive facilities, labor and expense, and it is necessary to establish propagation and feeding technologies for each targeted animal. It is also necessary to have planned breeding and selection in order to maintain genetic characteristics. There are many problems that must be quickly resolved to understand the ideal basis for meeting this objective and to develop technologies for specific manipulations.

With the aims of efficiently propagating domestic animals and fish and of obtaining highly productive animals by using genetic control, artificial insemination with preserved sperm (semen) or the preservation of the egg, separation and implantation are widely practiced. The freezing of reproductive cells which are important elements in this process is being effectively used as a technology for the preservation of genetic resources.

Technology for the freezing of sperm was first developed for cows, and currently it has been successfully used for swine, goats, chicken, and some fish such as red sea bream and flounder. There have been reported successes with the freezing of bovine and swine eggs. With cattle, the goal of conducting an egg supply operation as an actual means for propagating domestic animals is already being achieved, and it is anticipated that this will become a technology for the preservation of genetic resources. Moreover, this technology is being tried on experimental animals like mice and rats, and it is being applied to animal preservation and nurture within established systems.

Recently, technologies for preservation via tissue and cell cultures are also gaining ground, and it is possible to freeze subcultures and established stock of removed cells for all kinds of animals including human beings. Yet applications are limited because animals differ from plants in that it is generally difficult to regenerate individual animals. However, DNA as the genetic substance in the nucleus and cytoplasm has a wider range of application than DNA fragments because it can be maintained on the species level of the organism which supports the individual. The necessary technological development is underway that will make the operation of cell banks routine. The problem of changes in tissues and cells under cultivation is the same as with plants, and the guarantee of genetic stability in the development of culture technology and in freezing is an important issue under study.

Because the freezing of DNA fragments can maintain specific genes in a stable manner over a long period of time, it is expected that the applications of this to the advancement of genetic manipulation technologies and to the preservation of genetic resources will expand more and more. Currently, because it is not always easy to regulate the DNA fragments of specific genes, it is limited to certain specific genes—for example, oncogenes—that are undergoing research and development. The preservation of genes used to directly participate in the production of substances will have to wait for future research and development.

4) Methods of Preserving Microorganism Genetic Resources

With the development of biotechnology in particular, the multifaceted variations in microorganisms has opened possibilities for the active use of the microorganisms

themselves, and for using their genetic materials even in higher order plants and animals. The importance of microorganisms as a genetic resource is a step ahead, and their preservation is also progressing at a feverish pace.

The preservation of microorganisms differs from that of plants and animals inasmuch as they are preserved as a strain which is a collection of many bacterial bodies, and the important goal is to maintain their special characteristics as strains. That is, because the individual bacteria which compose the strain are not necessarily genetically uniform and because they may have characteristics that easily change due to environmental conditions, a high degree of specialized knowledge is required in order to preserve their characteristics as a strain over a long period of time. With this in the background, research into the methods of preserving microorganisms has advanced remarkably in recent years. In addition to freezing, the development of preservation methods such as ultra low temperature freezing has gained ground, and the long term storage of many microorganisms is now possible. The facilities of organizations which preserve culture collections of microorganisms as genetic resources are being operated around the world. On the other hand, however, long-term preservation has proven difficult in some actinomycetes, filamentous cells, animal protozoa, mycoplasmas, viruses and marine micro-algae, and even among microorganisms that can be preserved, some have trouble maintaining stabilized characteristics and some have an extremely low survival rate during preservation. Thus, many unresolved technical problems still remain.

The methods for preserving microorganisms are as variable as the types involved, and a variety of methods are being developed. Roughly dividing the methods, there are succession cultures, fluid paraffin layering, chilling, liquid suspension, hosting, drying and freezing. Among drying methods there are freeze drying, L-drying, gelatin disk drying, disk in bag, silica gel drying, magnetic beads, paper disk, and soil drying, etc.; and among freezing methods there are liquid nitrogen freezing, refrigeration, and other more detailed distinctions. In these conditions, because an extremely wide range of organisms such as filamentous cells (spores, hyphae), yeasts, bacteria, actinomycetes, micro-algae, protozoa, bacteriophages and viruses is included in the groups of microorganisms to be preserved, and because these reflect conditions which include many sub-classifications within the groups, it is necessary to consider the characteristics of the method of preservations (advantages and disadvantages), the research and experiment goals, and the facilities, equipment and personnel available when selecting the method of preservation.

Recent developments in cryobiology have been successfully used in the field of microorganism preservation. We have already reported that there are far-reaching possibilities for the application of ultra low temperature technologies for the preservation of bacterial strains, and that this method is being positively adopted as a long-term, stable preservation technology. There have also been attempts at using liquid nitrogen to freeze filamentous fungus that have been made into protoplasts.

Furthermore, there have also been attempts at the subculture, freezing, and the cryopreservation of virus particles and such small organs within the cell as plasmids, and there have also been attempts to freeze and preserve DNA and RNA fragments at low temperatures. As with plants and animals, the current methods for preserving microorganism genetic resources are extremely varied.

2. Uses of Genetic Resources

(1) Current Uses of Genetic Resources

The use of a genetic resource is related to the inner and outer objectives for the collection and preservation of the living organism as a genetic resource. The principal concerns involved are resources with targeted uses, resources indispensable to fundamental research in science and technology, resources with uses highly valuable for industry and environmental protection, and resources expected to have latent use value. However, resources that may be lost, resources that are uniquely possessed or exclusively developed by Japan, resources used in the past, and resources valuable for their scarcity are also targets of preservation. Because the principal aim of preserving and handing down these latter resources is because of their cultural heritage rather than their use, they are important resources to preserve, even if, with a few exceptions, they are infrequently used.

Ordinary experimental organisms, the genetic resources important to fundamental research in science and technology, are preserved and used at the universities and attached research facilities primarily responsible for basic biological fields. Among these, there are fields that try to understand the phenomenon of life within living organisms on the molecular level as the foundation of the life sciences, there are fields which utilize these results and develop biotechnology to establish improved technologies that center on living organisms, and there are fields of fundamental biological research which attempt to advance beyond the traditional academic system of biology.

Recently, along with the rapid development of molecular biology, such fundamental life phenomena as heredity, generation and differentiation, cell propagation, the composition of form, growth, reproduction, aging, immune functions and brain and neural functions have been explained on the molecular level as processes manifesting the form and substance of genes. Moreover, there is a strong tendency to transfer the important points of research to the development of technology that manipulates genetic information. The development and use of beneficial experimental organisms has been flourishing in this kind of research.

From this perspective, the drosophila which played a great role in past genetic research, and the nematode and shiroinunazuna [phonetic] which have come to be highly regarded in the development of recent molecular biology

have laid the foundation for the research achievements in genetics and cytology up to the present. Thus, in order to explain the phenomena life on the molecular level, an importance is attached to felicitous genetic resources. Moreover, the *E-coli*, Bacillus subtilis and agrobacteria which have played a significant role in the development of genetic manipulation technology are also important, as are the microorganisms and the cultured animals cells that have been used in the development of cell fusion technologies. Because not only microorganisms but higher order plants and animals have recently been converted in form and substance, the range of experimental organisms that are used for fundamental research in the field of molecular biology has grown rapidly.

In the fields related to health and medicine which are directly connected with the life support of human beings, the role played by experimental animals is enormous. The mechanisms of immunity, aging and the generation of genetic diseases, cancer and a variety of other illnesses, etc. have been explained on the molecular level. In order to apply the results of this to new methods of prevention, diagnostic methods and therapies it is necessary to do corroborative research on test organisms before such methods can be used on humans. In these instances, experimental animals play a double role: They substitute for humans in order to study the influence of external physical, chemical, or biological factors on the extension of human life; and they are used in the development of pharmaceuticals and diagnostic drugs to evaluate the efficacy and safety of chemical substances. In addition to primates such as monkeys, experimental animals that have made great contributions in this field include mice, rats, guinea pigs, rabbits, dogs, cats and hamsters.

Because industrial uses are directly related to the production of resources necessary to daily human life, this is the most important area quantitatively and qualitatively in terms of the use of genetic resources. In food-related areas, research materials for genetic breeding that form the basis for these resources include agricultural and horticultural crops, domestic animals, marine organisms, medicinal plants, forest resources, beneficial insects and beneficial microorganisms. All of these may be provided with such extraordinary characteristics as resistance to all kinds of pests, resistance to bad environmental conditions, high photosynthesis functions, and high yield functions. Because things grown in the wild can be included in the broad sense of breeding, all the organisms on the face of the earth can be seen as genetic resources. However, because there are limits to our capacity to preserve them, a fixed standard of selection is necessary in the preservation of organisms as genetic resources, and it is organisms falling within that scope that will be used.

In the resource and energy industry, energy is produced from biomass and solar energy is converted from resources utilizing living organisms. The use of genetic resources in this field entails the reevaluation of materials already being preserved; however, the focus will be placed on the positive search, collection, and evaluation of resources from a new standpoint. Moreover, in the chemical industry, the focus is on the selection and use of beneficial microorganisms in order to develop and produce chemical products such as pharmaceuticals that principally use microorganisms, diagnostic drugs, and enzymes. All kinds of microorganisms are found in the fermentation industries: microorganisms and enzymes are used in bioreactors and some important genetic resources help improve productivity and efficiency, such as substance production by cell culture and seeds and seedlings production by tissue culture. The range of uses for genetic resources is diversifying, and the key to business success is the selection of seeds and varieties that correspond to use objectives.

In environmental protection, there is the maintenance of atmospheric composition by the protection of forests and of the green belt on a global scale. There are also many aspects in the sphere of daily human life that depend on the use of genetic resources. For example, living organisms are used in order to clean up or undo the damage wrought by eutropic waters containing many organic compunds, nitrogen, and phosphorus, nondegradable substances, toxic heavy metals, and toxic gases, etc. Microorganisms are being developed and used to improve land polluted by residual agricultural chemicals, and flowering trees and green plants are used to maintain and promote a positive and more favorable environment.

(2) Distribution of Genetic Resources

This was touched upon in the section on preservation conditions. The research institutions that preserve and distribute genetic resources in Japan are mostly those attached to government ministries, agencies, and universities. Each manages its operations independently according to the variety of organism, the importance of preservation, the use objectives or the administrative division.

The Ministry of Education has been appropriating a budget for species preservation operations at the national universities ever since FY52. In 1987, it supported a total of 77 research institutions with these operational funds—26 for animals, 23 for plants, 21 for microorganisms, and seven for animal cell strains. These research institutions preserved and managed either specific or multiple varieties of organisms. Each institution is a specialized center of traditionals, several have attained worldwide acclaim and high evaluations for their famous collections.

Moreover, the Research Center for the Preservation of Genes and Experimental Organisms and the Genetic Information Research Center of the National Institute of Genetics began operations in 1985. These research institutions were established for joint use by all universities, and they are responsible for R&D and the general maintenance of experimental varieties of animals, plants, and microorganisms. Furthermore, even when

there is no budgetary policy for these kinds of systematic species preservation operations, there are many who are independently preserving experimental organisms in university botanical gardens, herb gardens, experimental forests, farms, research groups and research labs. Not only do they use these materials for their own research, but a great many offer experimental materials when requested by researchers.

The Science and Technology Agency began upgrading development operations of an information system for the preservation and distribution of microorganisms when it established the Center for the Preservation of Microorganism Species at the Institute of Physical and Chemical Research in 1981. In 1986 it opened a facility for the preservation of cells and genes, and it continues to promote the collection, preservation, and distribution of cell and genetic materials consistent with the fundamental arrangements for life science research.

The Ministry of Health and Welfare preserves and distributes medicinal plants at the test stations for the cultivation of medicinal plants of the National Institute of Hygienic Sciences, and it also preserves and distributes experimental animals at the Primate Center of the National Institute of Health. Recently, it established a Cell Bank at the National Institute of Hygienic Sciences and a Gene Bank at the National Institute of Health. It is promoting operations to preserve and distribute genetic resources on the cellular and genetic levels under the conception of a Research and Resource Bank.

The Ministry of Agriculture, Forestry and Fisheries has always had responsibility for the improvement of crops and domestic animals. Because they have poured energy into the preservation of genetic resources as breeding materials from the standpoint of raising and offering new varieties or organisms for the agriculture, forestry, horticulture and livestock industries, they have numerous technical achievements in culturing many kinds and varieties of organisms. Based on these results, they have promoted the operation of a gene bank related to general agriculture, forestry and fishery organisms since 1985, and they are giving a positive impetus to the preservation, evaluation, development, and distribution of domestic animals, crops, microorganisms, forest trees and marine organisms, etc. They publish a catalogue of preserved organisms, and by setting up distribution regulations related to the sale of organism varieties preserved among their holdings, they have established a system of distribution that can respond to requests from the general public.

The Fermentation Research Institute of the Ministry of International Trade and Industry, as a Patented Microorganism Depository, combines its role as an international depository organization with the custody and distribution of patented microorganisms. The National Institute for Environmental Studies of the Environment Agency has also set up a facility for the preservation of microorganisms, and it primarily preserves and distributes algae.

Other organizations specializing in the preservation and distribution of microorganisms are the National Research Institute of Brewing of the National Tax Administration Agency and the cell culture facility of the private corporation, the Fermentation Research Institute.

In addition to the above, there are a few other public research institutions, semi-private laboratories and private business laboratories that preserve genetic resources and will sell them upon request.

(3) The Present Status of the Distribution of Genetic Resources

Accompanying the thriving research and development in biotechnology, there has recently been a sudden heightening of concern for genetic resources, and inquiries to the preserving organizations about the species available and requests for their distribution have shown an increasing trend.

According to a 1988 survey given by the Science and Technology Agency to organizations preserving plant genetic resources, among the 460 organizations giving effective responses relating to information and equipment, the percentage of organizations receiving such questions were: 68% had inquiries about the release and distribution of preserved plants; 52.4% about preservation conditions; 40.4% about the characteristics and classification of plants; 34.3% about methods of use; 14.1% about passport data; and 19.9% other. This clearly indicates how preserving organizations are being approached with many inquiries aiming at the use of preserved plants. The previous numbers indicate the frequency that inquiries come in. If we look just at the frequency of requests for release and distribution, we can get a better idea of the organizations that receive this kind of request: 72.4% of the organizations receive several requests annually; 21.8% receive an average of five requests per month; 4.8%, 6-10 requests; 1.0% 11 requests or more. Statistics indicate that experimental animals such as mice, rats, guinea pigs and rabbits are used on the order of more than 100,000 to several million a year. Other experimental animals are certainly used in great quantities too, but the details are not known. Statistical resources are not available as to the number of microorganism and plant genetic resources that are actually used. Thus, the resources that are publicly recorded from the two or three sample organizations below indicate but a fraction of the actual distribution.

After 2 years of experimental sales distribution, the Center for the Preservation of Microorganism Species of the Institute of Physical and Chemical Research began actual sales distribution in 1986. The number of distributed strains increased at an accelerated pace with an actual sales distribution in 1987 of 1,709 strains (1,539 domestically, and 170 strains abroad).

The test stations for the cultivation of medicinal plants of the Ministry of Health and Welfare exchange the seeds

of medicinal plants with over 70 nations worldwide, and its distribution records show: 1,726 varieties to 365 organizations in 72 countries in 1980; 2,600 varieties to 370 organizations in 74 countries in 1981; 2,900 varieties to 380 organizations in 74 countries in 1982; 3,701 varieties to 395 organizations in 76 countries in 1983; 3,711 varieties to 409 organizations in 76 countries in 1984; 4,567 varieties to 410 organizations in 76 countries in 1985; and 3,720 varieties to 411 organizations in 76 countries in 1986. The second three years showed a slight increase over the first three years.

The distribution records for plant genetic resources in the operations of the Gene Bank of the Ministry of Agriculture, Forestry and Fisheries were: 4,308 varieties in 122 transactions in 1983; 6,773 varieties in 175 transactions in 1984; 6,510 varieties in 330 transactions in 1985; 7,141 varieties in 282 transactions in 1986; 12,138 varieties in 331 transactions in 1987; and 5,745 varieties in 239 transactions in 1988. Here too, there has been a slight increasing trend recently. The totals for the number of distributed species above indicate that 1987 was the year of greatest distribution. When looking at the recipients of these distributions and the internal contracts for distributed plants, there were 9,658 varieties in 130 transactions distributed to national experimental research organizations (79.6%); 150 varieties in 10 transactions to public research organizations (1.2%); 356 varieties in 39 transactions to universities (2.9%); 423 varieties in 57 transactions to private parties (3.5%); and 1,548 varieties in 92 transactions abroad (12.8%). The research organizations belonging to the Ministry of Agriculture, Forestry and Fisheries were included in the national organizations which had the greatest distribution. When categorizing the varieties of plants, there were 806 varieties of rice in 74 transactions (6.6%); 3,920 varieties of wheat in 58 transactions (32.3%), 4,934 varieties of beans in 46 transactions (40.6%); 32 varieties of potatoes in eight transactions (0.3%); 415 varieties of minor grains and special crops in 18 transactions (3.4%); 1,176 varieties of fodder and feed crops in 30 transactions (9.7%); nine varieties of fruit trees in five transactions (0.1%); 845 varieties of vegetables in 91 transactions (7.0%); and one kind of flowering tree and greenery in one case (0.0%). In this year the number of beans and wheat distributed were remarkably high.

The results of the distribution of microorganisms by the member organizations in the Japan Association for the Preservation of Microorganism Strains were reported in their October 1988 proceedings. Leaving aside the six organizations that did not respond, the 19 member organizations distributed 18,176 strains in 3,459 transactions domestically, and 1,084 strains in 275 transactions for a total of 19,260 strains in 3,734 transactions.

The Microorganism Center of the Ministry of Agriculture, Forestry and Fisheries' Gene Bank distributed 86 strains in 26 transactions in 1987, and 272 strains in 73 transactions in 1988. These numbers are not included in the statistics for the association mentioned in the previous paragraph. When classifying the numbers for 1988 in terms of distribution destinations, 97 strains went to national testing laboratories in 19 transactions, 18 strains to public testing laboratories in 14 transactions, 84 strains to universities in 13 transactions, 72 strains to other private groups in 26 transactions, and one strain to one foreign country. When classifying the numbers in terms of types of microorganisms, there were 114 strains of bacteria in 31 transactions, 135 strains of filamentous bacteria in 25 transactions, 11 strains of plant viruses in six transactions, 10 strains of animal viruses in nine transactions, and two strains of protozoa in two transactions.

(4) Management of Genetic Resources Information

The most important business conducted at organizations which preserve genetic resources is the management of the lineage of the organisms as a "strain" and the management of the "information" which accompanies this. When receiving or distributing a strain, if vital and sufficient information does not accompany it, it cannot be adequately managed and its use value as a genetic resource is not very high.

The minimum information necessary for genetic resources is the genus name, the species name and the type or variety name which indicate the classification of the organism. Other fundamental information would include passport data that clarifies the source and history, and other necessary management information such as that regarding the receipt, preservation, propagation and distribution of the strain. Next in importance is biological data which is basic to the classification, genetic, physiological and ecological data accumulated by research and development. Physical, chemical and biochemical data is also necessary information when used in scientific and technological research and development. In terms of industry, it is also important to have data related to the special conditions when used by agriculture, forestry, fisheries, and the chemical and fermentation industries. It is also necessary to have data related to the resource value (process and use) from the standpoint of using these products. Additionally, in terms of environmental safety, it is important to have information related to keeping the environment clean. Moreover, now that the objectives of the preservation of genetic resources have been widened, it is essential to have ethnobiological data, specifically, information relating to the cultural evaluation of genetic resources.

In a survey of organizations preserving plant genetic resources conducted by the Science and Technology Agency in 1988, 39.3% of the 491 responding organizations were recording only the plant name or common name, and this was the highest response level. Meanwhile, 16.3% were preparing to record further agricultural data; 13.5%, passport data; a total of 11.2% were recording genetic, physiological and ecological data or physical, chemical and biochemical data; and 8.1%, botanical data. However, because these figures include some organizations that have not yet started recording

this information, the upgrading of information about plant genetic resources is probably not quite this advanced yet.

Moreover, the methods of managing the information were also studied. Some 29.3%, the highest response of the organizations, keep records with a preservation ledger. Next, 23.3% of the organizations draw up a catalogue (of these, 11.8% were printed and published), 18.7% make simple memos, and 8.6% use cards. The bulk of these are a long way off from using modern data processing systems. Recently, the use of computers has been increasing, but even if those with future plans are included, this amounts to only 13.2%. Among these, those who intend to streamline management by putting it on a database are no more than 5.2%. With the rapid spread of personal computers, it is expected that this number will increase rapidly. However, one cannot avoid the feeling that despite all the talk of the information society and the high speed information society, to a surprising degree it has not yet invaded the field of genetic resource information management.

The goal of systematizing genetic resource information management is not only to effectively use the information in each of the preserving organizations, but it is also to make it public and offer necessary information to a broad range of general users. Currently, there is no organization or system that comprehensively deals with publicly offered genetic resource information. One must rely on printed media such as lists and catalogues that are drawn up and published by individual organizations. However, a prototype for a genetic resource information management system presupposes a database and a communications network using the recent advances in computers, communications equipment, and information processing technology. Because there have been some remarkable achievements in this regard, we will briefly summarize them.

In formulating a consistent policy to secure biological resources, the Science and Technology Agency established the "Investigative Committee To Provide Plant Genetic Resource Information" in 1980-81. It promoted the study of a plant genetic resource information database, organized its conception of the preparation and exchange of information, and outlined a suitable structure for such a database including the subject scope, listings and headings, data collection and database structure, database management and future development. Building upon these studies, it conducted a survey of information systems and investigated the actual conditions at preservation organizations (1987), designed a database (1987), and built, tested, and made a general evaluation of an experimental system (1988). As a result, it is possible to gather and organize an extremely wide range of information concerning the organizations preserving plant genetic resources in Japan, the actual preservation conditions, and currently available information. In addition, a system prototype necessary for the construction of a database of plant genetic resource information was developed for personal computers and CD-ROM.

A "Survey Study of Experimental Organism Information Systems" was conducted in 1976 by the Life Science Promotion Department of the Institute of Physical and Chemical Research that is controlled by the Science and Technology Agency. Development of an information system relating to six kinds of experimental organisms (experimental animals, microorganisms, plants, algae, animal cell cultures and plant cell cultures) was begun in 1978. Because the objective for the development of this system was the collection, evaluation, storage and release of information relating the characteristics and locations of all kinds of experimental organisms, an information processing field was added to the six previously mentioned fields, thus providing a total of seven specialized divisions. This information processing system was developed allowing for the special characteristics of each field. Since 1983 it has also participated in the joint international operation of a data bank on immuno-active substances such as hybridomas and monochronal antibodies. In 1986 this became the International Data Center of the International Alliance for the Preservation of Microorganisms, and it began operations of a data bank for worldwide collections of microorganisms.

In 1984 the Ministry of Education established a Genetic Resources Research Laboratory at the Center for the Preservation of Genetic Experimental Organisms of the National Institute of Genetics. This research laboratory was the center for conducting developmental research on information management systems for experimental organism varieties, and for organizing such team research as the "Study of Systematizing Information on the Varieties of Experimental Organisms" (1983-85), the "Study of Developing Information about Varieties of Experimental Organisms" (1986-87), the "Study of Creating a Common Database" (1988). The results of these efforts were brought together in the "Varieties of Experimental Organisms in National, Public, and Private Universities." Data was collected concerning the department preserving the organisms, the personnel in charge, the species of organisms and the number of varieties, etc. for all the varieties of experimental organisms being preserved at each organization. This was published as a basic resource. By making a database out of the fundamental data, an ongoing data management system was established. Moreover, in cooperation with Kyushu University, data about experimental varieties of silkworms were arranged in relation to the preserving organization, the varietal name, the genetic composition and the party obtaining them. This resource was made public, and the data was made into a database.

The Agriculture and Forestry Department at the University of Tsukuba conducted "Search, Collection, Preservation and Evaluation of Japan's Native and Introduced Crop Genetic Resources" in 1979-1981 and "Search, Preservation, Evaluation and Use of Crop Genetic Resources" (1983-1985). The native information about

the crop genetic resources preserved in the fields at each university were organized, a loose leaf catalogue was drawn up and a database was constructed on a large scale computer.

The National Institute of Hygienic Sciences of the Ministry of Health and Welfare arranged the 197 genuses, 2,857 species and 4,977 varieties (1987) of medicinal plants preserved by the five national experimental stations for the cultivation of medicinal plants according to scientific name, common Japanese name, preserving organizations, introducing organization, and year of introduction, etc. A catalogue was drawn up and a database was constructed on a personal computer. In "Visions of Medicinal Plants," such information as name, availability, medicinal effect, components, shape characteristics and cultivation management can be processed by image information of six classifications. In the "Register of Medicinal Plants," management data, characteristics data, research data and specimen data can be divided into three forms, namely, card, table, and map.

In the operations of the Gene Bank of the Ministry of Agriculture, Forestry and Fisheries as well, mass production of valuative data on all varieties runs concurrently by a special valuative operation for agricultural, forest and fishery organisms. Rapid progress is being made in the construction of a database for characteristics data, passport data and management information at the central bank. Here, while maintaining tight-knit cooperation with the public organizations in the urban and rural prefectures, the ministry aims at a total national system for agricultural, forest and fishery products. Moreover, the ministry has set up a large scale computer in a dedicated use computing center for experimental research organizations. Because this establishes a support system for research activities via an online network linking research organizations under a national umbrella, there is the possibility of real time use while researchers remain in their own laboratories. Consequently, the ministry is establishing a system that can effectively use genetic resources not only for breeding and fundamental research, but for all research fields relating to agricultural, forest and fishery organisms. It is expected that in the future full use of the database will be made by further building the database and by encouraging thorough training in its use.

Besides these, independent information management systems for genetic resources are being developed by individual organizations, departments, divisions, and research laboratories, and these are being promoted by public genetic resource centers and private organizations. Because personal computers have become commonplace and offer the development of easy to use database systems, the mutual exchange of information that has been independently accumulated, and the creation of a network capable of doing this will probably be important problems to face in the future.

Even thinking in terms of the distribution of genetic resources in the form, not of the genes themselves, but of converted information, many challenges still confront the management of genetic resource information. The development environment for the information management system, including hardware equipment and software development, must be improved. There are many problems from the standpoint of data production. There are also issues that need to be dealt with in the future to improve such conditions as: the standardization of survey items and survey criteria, the drafting of a characteristics survey manual for that purpose, the systematization of data collection, the organization of operations management, and the creation of a network.

3. The Transition to a National Policy and the Preparation of a Preservation System

In the section on the present conditions of the preservation and use of genetic resources, we touched on national administrative policies in a fragmentary way in the description of the policies of all the government ministries and agencies for the security of organisms as genetic resources. Here, we will summarize the developments closely related to this problem, the administrative response, and the gradual progress toward completion.

The initial period in which the importance of preserving varieties of organisms was emphasized and a national policy was positively promoted came in the 1950's. At that time, there was an urgency to rebuild world agriculture: With a world food shortage looming in the background, great strides were being made in food production by the development of of high performance varieties. The collection and preservation of important common species and existing varieties was strongly advocated for the international exchange of materials necessary to improve crops and livestock and for the development of new varieties.

The next period came after 1965 when the phenomena of genes which are the basis of the life sciences was explained on the molecular and cellular levels. Symbolic of this was the report of the Science Council, and advisory organ to the prime minister, "On Establishing a Center for High Order Organisms and Expanding and Strengthening the Facilities That Preserve Individual Varieties." The Ministry of Education and the Ministry of Agriculture, Forestry and Fisheries, etc. began operations to fulfill this purpose corresponding to the jurisdiction of each. The conventional system was strengthened and steady progress was planned. Moreover, many researchers came to realize the importance of genetic resources and the significance of maintaining and preserving them through participation in joint research on an international biological program. These researchers vigorously supported the advancement of policy to keep pace with the technological developments in related fields.

Today then, we are facing a third important period, which should be called one of completing the tasks at hand. The security of genetic resources is recognized as the indispensable fundamental condition for life sciences

and biotechnology research and development. The first direct steps to the promotion of specific policies came in questions 10, 11, and 12 "concerning the basic research and development plans for advanced and basic technologies in the life sciences," in the April 1984 report by the Council for Science and Technology, as well as in the June 1984 Resource Council report question "concerning a security policy for living organisms as genetic resources" that was directed to the Director-General of Science and Technology Agency. Further, question 16 "concerning basic policy regarding upgrading the foundation for the promotion of science and technology," in its December 1989 report included among other things the completion of a system for the discovery, preservation, and supply of materials for research on organisms and the completion of a system for the preservation of genetic resources. In the background to the issuing of these reports were the scientific and technological development of the life sciences and biotechnology relating to living organisms, the rapid disappearance of life resources advancing on a global scale, pollution and destruction of the environment accompanying development, the exhaustion of underground resources and natural resources, a reconsideration of renewable living resources and the expectation that there is no limit to the capacity for development. The recognition of the urgent need for a positive policy was heightened to a remarkable degree, and such a policy has gained significance as a vital issue for today.

In the historical changes cited above, each government ministry and agency promoted the collection and preservation of varieties of living organisms relating to its own jurisdiction, and the security of genetic resources was been taken up in a positive manner as a policy issue. The principal policies of the government ministries and agencies follow.

Although it does not directly set the policy of the nation, the role played by the Science Council of Japan is important from the standpoint of supporting such a policy. The Science Council prepared the "Proposal for the Establishment of the Center for Microorganism Strains" in March 1967, and "On the Improvement of Procedures for the Preservation of Varieties in the Biological Sciences" in May of the same year. Building on these, it issued a recommendation to the prime minister "On Establishing a Center for High Order Organisms and Expanding and Strengthening the Facilities That Preserve Individual Varieties" in December 1968. The Subcommittee on Genetic Resources (1966-1982) established by the Science Council was directly related to the drafting of the recommendation mentioned above and continued indirect support activities toward its realization. As the Liaison Committee for Genetic Resource Research, it has been involved in instructional activities promoting the importance of genetic resources since 1984.

The Science and Technology Agency has taken responsibility for proposals relating to basic policies concerning the security of genetic resources from the standpoint of coordinating the science and technology policies brought about by all the government ministries and agencies. The Science and Technology Agency has played the role of the business office for the report by the Council for Science and Technology and for the report by the Resource Survey Committee. As a consistent follow-up to the report from the Resource Council, it has conducted a Survey of the Present Status of Preservation Organizations and a Survey for the Development of an Information System Prototype through the Survey Project for the Formation of Policy on the Preservation of Resources and Living Organisms.

Moreover, the Science and Technology Agency has obtained the participation of all the related government ministries and agencies via Special Coordination Funds for Promoting Science and Technology, and it has promoted policy to secure genetic resources by conducting "Research on Technology for the Integrated Development and Use of Tropical and Sub-Tropical Microorganisms and Plants" (1981-83) and the "Survey on the Search for and Use of New and Useful Genetic Resources Through the Cooperation of ASEAN Countries" (1984-86).

In addition, under the aegis of the Institute of Physical and Chemical Research, it has made positive contributions intimately connected with genetic resources through the development of the Experimental Organisms Information System (1978-), the Facility for the Preservation of Microorganism Varieties (1981-) and the Facility for the Preservation of Cells and Genes (1986-).

The Ministry of Education includes the preservation and use of genetic resources in the part of its operations for the collection and preservation scientific materials that falls under the jurisdiction of the Scientific Information Division. It has promoted the preservation of experimental animals at the national universities since 1952 via expenditures for the preservation of varieties. It began these operations with a total of eight organizations (two for animals, two for plants, and four for microorganisms), and a total budget of ¥6 million. As of 1987, the total number of organizations leapt to 77 (26 for animals, 23 for plants, 21 for microorganisms and seven for animal cell strains), and it operates on a budget of ¥125 million for the securing of living resources. In 1990 it will have a projected increase in the budget up to ¥140 million.

As a result, such operations as the maintenance and preservation of varieties, development, special surveys and information management at the laboratories of universities and research institutes that preserve genetic resources as experimental organisms or at attached facilities can be funded from special expenditures for the preservation of species. Therefore, little pressure is placed on research activities by these operations, and valuable research materials that have been assembled for research purposes will not be lost due to the transfer or

retirement of the professor in charge. Moreover, facilities related to preservation such as the buildings necessary for breeding, the storage warehouses for seeds, or the culture laboratories for microorganisms, tissues, and cells are constructed by these funds, and this advances the actual equipping of the system.

The organizations within the Ministry of Health and Welfare that preserve medicinal plants are the five culture and testing sites run by the National Institute of Hygienic Sciences. Currently, seeds are preserved at the seed warehouse in Tsukuba, and they are cultivated as plants at the plots and specimen gardens of the test sites at Hokkaido, Tsukuba, Izu, Wakayama and Tanegashima. The medicinal plant genetic resource warehouse at Tsukuba was completed in April 1986. It is equipped with short term, long term and extremely long term storage rooms. It has germination testing rooms and seeds and seedlings storage rooms such that the management system for seeds is arranged successively.

Responding to the worldwide exchange of culture materials promoted by the Food and Agriculture Organization (FAO), in 1953 the Ministry of Agriculture, Forestry and Fisheries began a system to collect and manage types and varieties as culture materials by establishing a research laboratory with special responsibilities for the preservation of varieties that had been developed as a part of the breeding experiments up to that time.

The "Project to Organize and Strengthen the System for Preserving and Introducing Seeds and Seedlings" was begun in 1965, and such facilities as seed warehouses, disease free hot houses and screened rooms for raising seeds were set up. The system for managing culture materials was completed and strengthened by creating a separate funding framework to cover operational expenses. Then, the "Fundamental Plan for the Cultivation of Crops" was adopted in 1975, the cultivation system was completely reorganized, and plans were made to expand and strengthen the cultivation technologies of the sub-department for genetic resources. This was moved to the Tsukuba Academic Newtown in 1978, a seed warehouse equipped with all the latest capabilities was built, and plans were made to complete the next steps in the organization of the preservation system and in management operations. Then in 1983, in cooperation with the international genetic resource management network promoted by International Board for Plant Genetic Resources (IBPGR) and the establishment of a seeds and seedlings method to protect new varieties, the "Plan To Establish an Integrated Management System for Crop Genetic Resource and Culture Information" was revised, and expenditures for management and operations which had been ¥50 million up to then was increased to ¥180 million in one stroke. Thus, the goal was set on the establishment of a genuine genetic resource management system.

The process described above outlines the policies to secure genetic resources in the crop related fields of the Ministry of Agriculture, Forestry and Fisheries. While these were appropriate, subsequent progress in the life sciences and developments in biotechnology created a situation in which those policies could not fully respond to the demands for the security of living resources related to other fields. Therefore, in 1985, the operations of an integrated gene bank that embraced all the fields related to agriculture, forestry and fisheries was given to the ministry. A Gene Bank Management and Operations Council was established within the ministry, and an organizational system was structured by having Center Banks set up at the testing and research organizations for plant, animal, microorganism, forest tree and marine organism genetic resources. Sub-banks for each field were also set up in the related organizations. Thus the scope and content of the system can fully respond to such demands of the times as the building of more seed storage warehouses and disease free hot houses, increases in operational costs and the enactment of operational regulations. The funds budgeted for the operational costs of the Gene Bank of the Ministry of Agriculture, Forestry and Fisheries increased steadily from ¥461 million in 1987 to ¥498 million in 1988 and ¥513 million in 1989.

The Seed Storage Management Laboratory responsible for the storage and distribution of seeds for cultivation was created in 1968. This research organization was revamped in 1983, thus creating the Genetic Resource Department in the Agricultural Life Resource Research Institute. Five research laboratories were established to study information systems for the search, introduction, preservation and evaluation of genetic resources. A management laboratory for the preservation of reproductive substances was also set up. Then, in December of 1986, the Genetic Resource Department was expanded and strengthened, and the Genetic Resource Center was begun in order to smoothly promote the operations of the Agriculture, Forestry and Fisheries Gene Bank. Research and development provided the basis for the consolidation of the general management of Center Bank operations and for the management of genetic resources. This was accomplished by the construction of a system with a genetic resource regulator, nine research teams in two departments, one information management division and one management division. Moreover, when the Seed Storage Management Laboratory started off, it had only three related employees, but as of October 1988, the director of the Genetic Resource Center had 55 employees underneath him performing genetic resource research, development, and management activities. This reflects a giant leap in the development of the organizational system.

This kind of administrative response by the Ministry of Agriculture, Forestry and Fisheries to form a policy for the security of genetic resources not only improves the system of research organizations, but it also establishes groups responsible for genetic resources under the appropriate divisions within the administrative departments and bureaus. Moreover, the position of a genetic resource manager has been established. This system promotes the general management and administration of

genetic resources, while maintaining close connections to related agencies and bureaus.

In addition to this, genetic resources are being independently collected and preserved by the urban and rural prefectures and by private businesses through the building of seed storage warehouses and the establishment of genetic resource centers and botanical gardens. Thus the policy for the securing of genetic resources is currently making wide scale progress in an orderly manner on the national and local levels.

4. Future Issues in Genetic Resources

The living organisms inhabiting the planet and the things they produce are resources. It goes without saying that these are indispensable for the survival of humanity, but only fairly recently have we come to label as "genetic resources" the group of organisms containing these genes (genetic information) within themselves.

As the phenomenon of life within living organisms is now scientifically explained, phenogenetics is now moving toward a molecular biology that grasps the specific cause and effect relationships between genes and forms as the result of the transfer of genetic information. Thus, the phenomenon of life existing in every living organism has come to be understood on the level of physical chemistry. This is what has set the stage for the epoch-making developments in the life sciences.

Consequently, the importance of securing genetic resources tends to be seen in terms of improving the fundamental conditions for the life sciences and for biotechnological research and development. At bottom, DNA holds all the genetic information that has been accumulated by the generation of species in the course of evolution from the birth of life on the planet up to the variety of organisms living today. This genetic information is passed down to following generations only through the multiplication and reproduction of existing organisms. It cannot be ignored that the use of this genetic information is a source that will give rise to limitless possibilities.

Moreover, by breeding species, which can be called the artificial control of the evolution of organisms, useful and important genes have been accumulated in the form of crops, livestock, and many experimental organisms that have contributed to the development of fundamental life sciences. The development of these organisms as maintained varieties is also important from the standpoint that once they are lost, it is impossible to recover them. The number of species on the way to rapid extinction is increasing at an alarming rate due to environmental destruction by human beings. Survival of humanity is possible only through coexistence with other living organisms, thus we must have a policy to secure genetic resources.

When collecting, maintaining, and managing organisms, there are many limiting factors—especially economic. Because there is a certain limit to the number and varieties of organisms that can be secured as genetic resources, it is important to establish standards for their selection. From the standpoint of developing new resource organisms and experimental organisms, there is the challenge of seeking out unknown organisms. Therefore, we cannot simply rely on previous standards: We must also evaluate latent resources and adapt to changing circumstances.

The next issuev is how to maintain organisms in a useful and beneficial form once they are secured and transferred to the management of human beings. This entails the management of organisms simultaneously with data management principally revolving around the production and processing of information concerning the support of the target organisms throughout its life span, genetic stability, propagation, and the analysis of special characteristics. The facilities and equipment for the technical development, operations and research necessary to smoothly promote this endeavor are also important. Furthermore, management operations need to be made systematic, routine and automatic, costs must be lowered as much as possible for all the energy, resources and space required, and operations must be thoroughly streamlined.

As previously indicated, each individual organization, ministry, and agency is updating the system for securing genetic resources. Because security policies are made on a national basis, it is expected that in the future these systems will be given general functions and that they will be linked together as a network. This kind of organizational system building is desirable from the international standpoint as a response to foreign organizations preserving genetic resources and from the domestic standpoint as a way to increase efficiency in preservation and improve convenience for users. For example, suppose that information on the genetic information currently preserved within Japan is placed into a unified information system. Such a system could play a fundamental role as the leading edge development of life sciences, and it could also contribute to the practical use of more obscure information and resources.

Finally, we must raise the vitally important issue of the training and securing of human resources for the management of genetic resources. Because high value resources can be maintained only by the use of superior personnel, human beings are the most important genetic resource available to sustain the leading edge in the life sciences and biotechnology. Human resources contribute to the development of the modern life sciences and have an important role to play in the survival of future generations.

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